FEVER

ITS THERMOTAXIS AND METABOLISM

ISAAC OTT

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BY

ISAAC OTT, A.M., M.D.

Professor of Physiology Medico-Chirurgical College, Philadelphia, Member of American Physiological Society, Ex-president of American Neurological Association, Consulting Neurologist Norristown Asylum, Member of the Deutsche Medicinischen Gesellschaft of New York, Member of Vereinigung Alter Deutschen Studenten in Amerika, American Society for Pharmacology and Experimental Therapeutics, Society for Experimental Biology and Medicine, Member of The American Association for the Advancement of Science, Corresponding Member of Atlanta Academy of Medicine, Member of Philadelphia Medical Club and Chemists' Club of New York, etc.

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Dedicated to the
Memory of my Father,
JACOB OTT

"Animalia in accessibus febrium intermittentium a principio frigore et horrore corripiunter sed paulo post majorem in modum incalescunt, quod etiam faciunt a principio in causonibus et febribus pestilentialibus."

"Qualis vero gradus sit caloris in cerebro, stomacho, corde et reliquis, similiter ad huc non est quaesitium." Bacon, Novum Organum. Lib. II, 13.

PREFACE

These three lectures were delivered before the Sophomore Class of the Medico-Chirurgical College. They have been thought worthy of publication, as the subject is one of maximal importance in the practice of medicine. The studies upon this subject have occupied the author for forty-five years, as a practitioner of medicine and a physiologist.

Isaac Ott.

ILLUSTRATIONS

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LECTURE I

FEVER, ITS THERMOTAXIS AND METABOLISM

LECTURE I

GENTLEMEN:—In the opening course of physiology for this year I shall invite your attention to a subject which will engage your minds every day that you practice medicine. I refer to fever. In my practice of many years it has been a daily, omnipresent factor. It is the alarm of the family, sometimes a sign of impending death and often a puzzle to the physician.

The process of fever has been a difficult problem for the last two thousand years. The fever may be a gentle wave, or every cell may surge, boil and burn, while the vibrations run to and fro until they overflow and the scissors of Atropos and the Stygian boat of Charon end all.

The questions now arise, What has thrown a strong man into fever? Why has the temperature suddenly run up? Where is the central point of this heat which is like a fire in his veins?

The study of fever includes bacteriology, immunity and pathological physiology. Aristotle thought heat was developed in the right heart; Galen placed its origin in the left heart, the so-called *flammula cordis,* and this was taught up to 1660. Bacon, in the "Novum Organum," defined heat as an expansive motion amongst the minute particles of bodies, which is the conclusion at which the most eminent physicists have arrived. Tyndall [1] quotes a considerable portion of Bacon's twentieth aphorism as illustrating the theory which he has himself so ably and clearly expounded.

In the seventeenth century, Van Helmont spoke of heat as produced in the

[1] Tyndall. "Heat and Mode of Motion." Appendix.

heart by a mixture of sulphur and the volatile salts of the blood.

Lavoisier, in 1775, first showed that the heat of animals was due to the combustion of oxygen. He also proved that the quantity of oxygen absorbed and of Co_2 excreted depended upon food, work and temperature. In 1783, Lavoisier and La Place [2] made calorimetrical and respiratory studies upon a guinea pig. Lavoisier also knew that nitrogen gas had nothing to do with respiration. These calorimetrical studies were followed by experiments with a water calorimeter by Crawford [3] and by Dulong and Von Despretz,[4] whose calorimeter is still a model for all subsequent water calorimeters up to the present day.

[2] "Lavoisier et de La Place Memoire sur Chaleur." 1780.

[3] Crawford. "Experiments and Observations on Animal Heat." London. 1788.

[4] Despretz. "Recherchés experimentales sur les causes de chaleur animale." "Annales de Chimie et de Physique." Tome 26; 1824. P. 337.

Then Regnault and Reiset,[5] in 1850, with their respiration apparatus studied the gaseous exchanges of animals, called indirect calorimetry. G. A. Hirn,[6] in 1857, studied calorimetry of man.

Brodie[7] held that the nervous system was the center of heat, whilst respiration cooled the animal.

LeFevre[8] has shown that the relation between the amount of heat and the amount of oxygen is not constant. D'Arsonval has shown that the curves of production of heat and the absorption of O are not concordant; in sleep, for example, the production of heat falls to a minimum, whilst the consumption of oxygen is not lowered to a corresponding degree.

Laulanié[9] found no fixed proportion be-

[5] Regnault et Reiset. "Annales de Chimie et de Physique." 1849.

[6] Hirn. "Recherchés sur l'equivalent mecanique de la chaleur." Colmar. 1858.

[7] Brodie. "Philosophical Transactions." 1811.

[8] LeFevre. "Chaleur animale." 1911. P. 76.

[9] Laulanié.

tween heat production and the respiratory gases exchanged.

Then Pettenkofer and Voit [10] built their splendid respiration apparatus and created in Munich the first school for metabolism, which has produced many workers now prominent in the scientific world.

But in the respiration calorimeter of Atwater [11] and Benedict we have direct calorimetry and indirect calorimetry (or the gaseous exchanges) combined. Their apparatus is nearly perfect for the study of animal heat and by its use they have again verified the law of conservation of energy and solved many other problems in metabolism.

Hence, the three methods of studying the phenomena of heat are: (1) by the thermometer (probably discovered by Galileo and used by Sanctorius), (2) by the cal-

[10] Pettenkofer und Voit. "Zeitschrift f. Biologie." 1866. Band 11, p. 478.

[11] Atwater. "A Respiration Calorimeter," 1884.

orimeter, and (3) by the amount of oxygen absorbed and the amount of Co_2 eliminated (indirect calorimetry).

THERMOTAXIS

Before we take up the subject of fever, I will call your attention to that of thermotaxis, which means heat regulation, so that the temperature is kept on an average for 24 hours at about 98.4° F.

Now thermotaxis depends upon four nervous centers: two basal thermogenic centers—the corpus striatum and the chief one, the tuber cinereum—and two inhibitory cerebral centers—the cruciate and sylvian.

In April, 1884, I [12] published amongst others the following experiments.

Experiment 2. Rabbit. Weight of animal 7⅗ pounds. (Here there was a transverse section of the corpora striata.)

[12] Ott. *Journal of Nervous and Mental Diseases.* Vol. XI, No. 2, page 141, April, 1884.

Time P. M.	Calorimeter Temp.	Rectal Temp.
12.25	84.86	101⅛° F.
1.55		104⅜° F.
3.15		104¾° F.
4.30		111½° F.
		Rise of 6¾° F.

Experiment 3. Cat; weight 5 11/50 pounds; transverse section through the middle of the corpora striata.

Time P. M.	Calorimeter Temp.	Rectal Temp.
12.25	74.50	102⅜° F.
1.40		102⅜° F.
2.30		106⅞° F.
3.45		107⅞° F.
		Rise of 4⅞° F.

It is from these and other experiments that I claim the discovery of the thermogenic center in the corpus striatum.

In October, 1884, Sachs and Aronsohn [13] published a paper, six months after

[13] DuBois. *Archiv. f. Physiologie*, Oct. 31, 1884.

mine, stating that there was a thermogenic center in the corpus striatum and that it was located mainly in the caudate nucleus. They also found an increased production of urinary nitrogen, an increased absorption of oxygen and an increased elimination of carbon dioxide. The increase of nitrogen in the urine they inferred was due to a using up of the protein. They did not make any calorimetrical studies to determine positively if the increase of temperature was due to increased production of heat or to diminished dissipation. They offered no proof, except gaseous exchange and the urinary nitrogen, of their conclusion that the rise of temperature was due to increased production of heat.

In September, 1887, Ott [14] and W. A. Carter (at that time a medical student) first showed calorimetrically that the rise

[14] Ott and Carter. *Therapeutic Gazette.* Sept. 15, 1887.

of temperature after puncture of the corpus striatum was due to increased production and not to diminished dissipation of heat. Thus in experiment 2, in a rabbit with a puncture into the right corpus striatum, the temperature rose 2.7° F., whilst heat production before the puncture was 13.70 B. H. units and after the puncture 22.50 heat units; heat dissipation before puncture was 16.68 heat units and after puncture 18.77 heat units. I first proved the existence of a thermogenic center in the corpus striatum and also first established the fact that the increase of temperature was due to increased production of heat and not to coincident diminished dissipation.

The claim of Richet [15] to have been the first to discover the thermogenic centers cannot be upheld. All that he claimed was that puncture of the anterior part of the

[15] Richet. *Bulletin de la Société de Biologie.* March 29, 1884.

brain produced hyperthermia due to increased production of heat.

There was no localization by him in the corpus striatum, but a cortical injury which Eulenburg and Landois before him had localized in the cruciate sulcus.

Barbour, H. G.,[16] has shown that the direct application of cold and heat to the region of the corpus striatum causes the rectal temperature to respond by a change in the opposite direction from that produced in that region of the brain. Cold (33° C.) applied to the corpus striatum causes a rise in the temperature of the body, associated with shivering and peripheral vaso-constriction. Centrally applied heat (42° C.), on the other hand, causes a fall in the body temperature.

Barbour and Wing[17] have also shown that the heat regulating centers are di-

[16] *Archiv. f. Exp. Path. und Pharmakol.* 1912, LXXXI.

[17] *Journal of Pharmacology and Experimental Therapeutics*, Vol. V. No. 2, p. 147.

rectly susceptible to the local action of drugs, both fever-exciting and anti-pyretic substances.

Barbour and Prince [17a] have shown that local heating of the corpus striatum in rabbits diminishes the Co_2 output, the oxygen combustion and the respiratory volume.

Local cooling of the same region gives precisely the opposite results.

Central heating reduces the temperature of the body not only by favoring heat dissipation but by diminishing heat production.

TUBER CINEREUM

In 1885, July 4, I [18] published a preliminary communication stating that a thermogenic center was localized at the anterior end of the optic thalami, and that the increase of temperature after puncture was due to increase of production of heat,

[17a] Barbour and Prince. *Journal of Pharmacology and Exp. Therapeutics*, Vol. VI, No. 1, page 1. 1914.

[18] Ott. *Philadelphia Medical News.* July, 1885.

as shown by the calorimeter. The temperature rise was especially marked when a puncture along the median line caused a peculiar shrill cry, a point to which Schiff first called attention, in the production of a sound.

In March, 1887, I proved that this rise of temperature was due to increased production of heat, as shown by the calorimeter, and not to diminished dissipation.

In July, 1891, I [19] showed that the center about the anterior ends of the thalami was more accurately located in the tuber cinereum. This was shown by the method of puncture.

I have also punctured the tuber cinereum in rabbits by means of a dental drill with a cross bar through the mouth and obtained a temperature of 109°. This section does not cut any thermogenic fibers.

[19] Ott. *Journal of Nervous and Mental Diseases.* July, 1891.

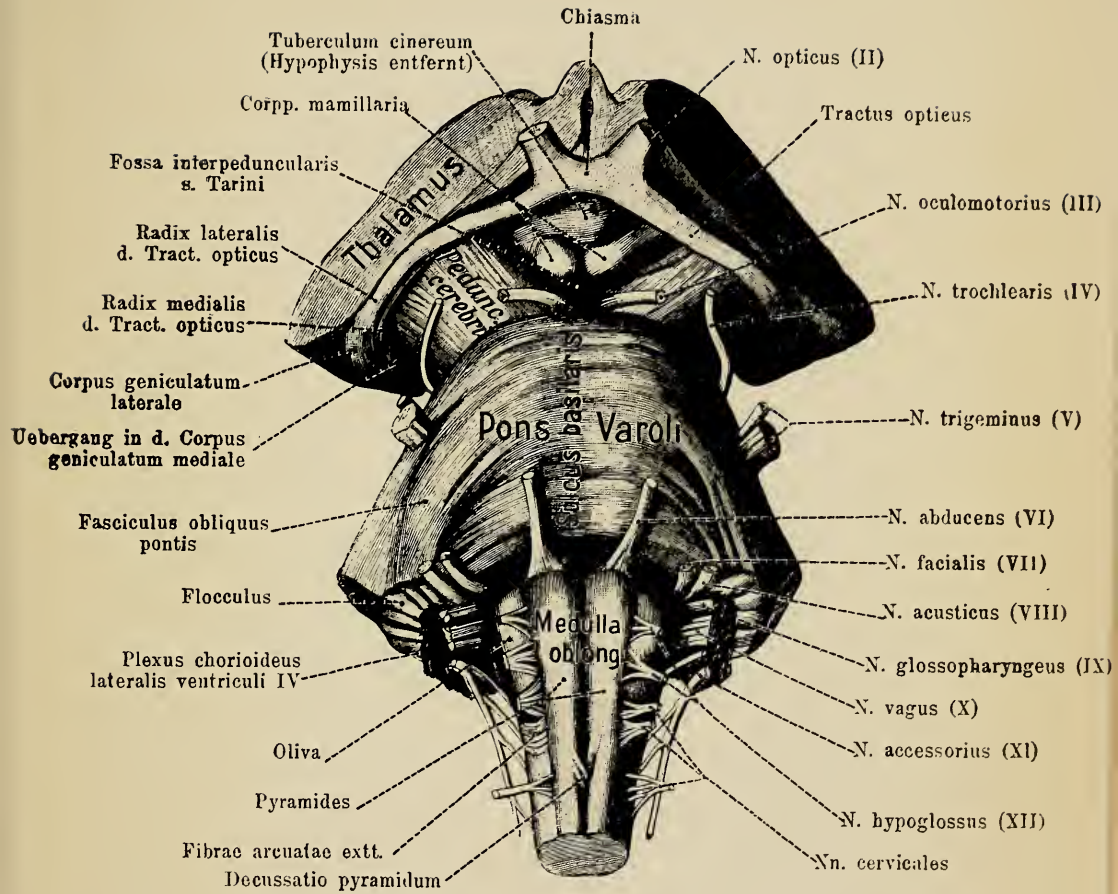

FIG. 1.
Showing Tuber Cinereum in Man.

Then Isenschmid and Schnitzler,[20] after a series of experiments, arrived at the conclusion that the regulation of temperature was mainly in the tuber cinereum in the rabbit; that the fibers which run from the tuber lie in the caudal part of the mid-brain, widely distributed in the ventral and median part of a transverse section. In the anterior part of the mid-brain they are not united in a compact bundle.

They also state that the corpus striatum is also concerned in heat regulation, but that it plays a subordinate part, for an animal without the corpora striata and cerebral hemispheres can regulate its temperature just as it normally does. They state that thermo-regulation depends mainly upon the tuber cinereum.

Jacoby and Roemer[21] have also made

[20] Isenschmid and Schnitzler. *Archiv. f. Exp. Path. und Pharmakolog.* Band 76. Heft 3 and 4. P. 202. 1914, May.

[21] Jacoby and Roemer. *Archiv. f. Exp. Path. und Pharmakol.* Band 70. 1912.

an interesting experiment by letting a minute globule of mercury into the third ventricle, which gave rise to a decided rise of temperature.

Streerath [22] believes the center in the anterior part of the thalamus is more powerful than the one in the corpus striatum.

J. Camus and Roussy [23] have found that a lesion at the base of the brain in the tuber cinereum produced polyuria. Their experiments were made on dogs after excision of the pituitary through the mouth. They state that in the tuber cinereum there is a zone which causes polyuria. This zone also has a regulating mechanism, which causes retention of water in the organism. Lesions in this region are able to produce polyuria with parallel polydipsia without disturbance of the mechanism

[22] Streerath. *Archiv. f. Physiologie.* 1910. P. 315.

[23] Camus and Roussy. *Comptès Rendus Société de Biologie.* No. 16. May 15, 1914. P. 773.

which causes retention of water in the system. In young animals it would appear that the regulating mechanism for the retention of water is less perfect than in adults.

Furthermore of all the disturbances which relate to the absorptional elimination of water, puncture at the base of the brain is more effective and durable than injections of urea, glucose, sodium chloride, caffeine, or a watery diet.

Bechterew and Sakovic[24] found that puncture of the tuber cinereum produced a rise of temperature and that this was due to increased heat production, as shown by Paschutin's calorimeter.

Sakovic also showed that the carbon dioxide elimination increased with the increase of temperature. Bechterew believes that the region of the tuber cinereum has an undoubted influence upon the tissues of the organism.

[24] Sakovic. "Dissertation." 1897. St. Petersburg.

Now Isenschmid and Krehl [25] have shown that heat regulation was destroyed by making sections in the mid-brain, that is, when the animal was placed in a warm chamber it could not prevent a rise of bodily temperature, or, in a cold chamber, could not prevent a fall of temperature; in other words, it acted like a cold-blooded animal, the temperature rose and fell with that of the air. They arrived at the conclusion that in the mid-brain a center existed which regulated the temperature of the body.

Citron and Leschke [26] found on mid-brain puncture that heat regulation failed, that cold lowered and heat elevated the temperature. They also found after "mid-brain puncture" that bacteria, protozoa, anaphylactic poison, sodium chloride, colloidal paraffin, and tetrahydro-beta-naph-

[25] Isenschmid u. Krehl. *Archiv. f. Exp. Path u. Pharmakol.* Band 20, 1912.

[26] Citron and Leschke. *Zeitschrift f. Exp. Path. u. Ther.* Band 14. 1913.

thylamine produced no fever, but a fall of temperature. They believe the seat of pyrogenesis to be in the mid-brain.

Cloetta and Waser [27] placed fine thermo-electric elements in the third ventricle. They also inserted thermometers in the rectum, in the anterior part of the cerebrum, under the skin and in other places. They then injected tetra-hydro-beta-naphthylamine into the circulation. The thermometric apparatus in the third ventricle showed a rise of temperature in a few seconds, whilst in the rectum, cerebrum and the other parts of the body the temperature began to rise later. Fever producing agents also greatly stimulated the thermogenic functions of the third ventricle.

As Isenschmid and Schnitzler have said, the chief nerve center in the regulation of heat is the tuber cinereum. It is the center where puncture causes rapid rise of

[27] Cloetta and Waser. *Archiv. f. Exp. Path. u. Phar.* 1913. Band 73.

temperature, much more rapid than after puncture of the corpus striatum. I have often punctured the tuber cinereum through the roof of the mouth in a rabbit, and within four minutes produced a temperature of 110° F. A great pyretogenic agent, tetra-hydro-beta-naphthylamine, can produce fever when the corpora striata and the cortex cerebri have been removed, as I have often demonstrated. Hence the conclusion that the tuber cinereum is the ruling center in the heat regulation of fever.

Cajal states that the nucleus of the internal capsule has cells which mingle with the cells of the tuber cinereum. To Cajal the tuber cinereum is a motor station placed upon the projection paths of the septum lucidum and of other systems of fibers whose origin is still not determined.

The tuber cinereum is the floor and anterior wall of the third ventricle and be-

longs, according to Cajal, to the pars optica of the optic thalamus. Its posterior or accessory nucleus resides between the mammillary eminence and the principal nucleus of the tuber. The tuber also has a superior nucleus and the fibrillary capsule on the surface of the nucleus hardly separates it from the rest of the hypothalamus.[28]

Edinger believes that the central gray matter of the mid-brain contains the central apparatus of the sympathetic. The afferent fibers of the mid-brain are the spino-tectal tracts running for all purposes in Gower's tract and ending in both anterior copora quadrigemina. The efferent tract of the mid-brain is the rubro-spinal. Hence the tuber cinereum has four functions: thermogenic, polypnœic, polyuric and vaso-tonic.

[28] Cajal. "Histologie du Système Nerveux." Vol. II, p. 48.

MINOR THERMOGENIC CENTERS IN THE SPINAL CORD

Spinal Cord and Co_2. I [29] have made experiments upon cats and rabbits, using d'Arsonval's calorimeter and Voit's little respiration apparatus. After section of the spinal gray matter or the spinal white matter at the junction of the dorsal and lumbar regions, there was an increase of temperature and an increase of carbon dioxide.

Spinal Cord and Heat Production. Ott and Collmar [30] have shown that section of the lateral columns of the spinal cord in the cat was followed by a rise of temperature which was accompanied by an increase of heat production and of heat dissipation, but that the increment of heat production was greater than that of heat dissipation.

[29] Ott. *Journal of Nervous and Mental Diseases.* Vol. XII. No. 4. October, 1885.

[30] Ott and Collmar. *Journal of Nervous and Mental Diseases.* Vol. XIV. July, 1887.

Spinal Cord, Its Partial Destruction, Effect on Heat Production. Ott,[31] in cats, destroyed by means of a stiff wire the spinal cord from the upper dorsal region downward; in sections and destructions above the fifth dorsal, heat production fell nearly one to two B. H. units, but afterwards rose to about one-third to one-half the normal output. If the injury was below the fifth dorsal, heat production nearly always remained but little below the normal amount, and in one case exceeded the normal amount. In this case there could be no spinal thermogenic centers connected with the cord from the fifth dorsal downward. Whatever spinal thermogenic center existed must have been in the upper part of the spinal cord, that is, the three pounds of the animal, for the anterior part (anterior to the fifth dorsal section), fur-

[31] Ott. Transactions of Pan-American Congress. 1893. Physiological section.

nished the heat. (Weight of animal was five pounds.)

Now, if we assume for the sake of argument that the heat produced after a section and destruction of the cord from the fifth dorsal is due to spinal thermogenic centers, with muscles and viscera, we must assume that the normal three pounds of the anterior part of the body with the spinal cord intact above the fifth dorsal vertebra can produce as much heat as the normal five pound animal with an intact nervous system. This view would be absurd. It is probable that all the heat is produced in the muscles and glands and that the spinal thermogenic centers are weak.

That no thermogenic centers of a marked thermic capacity exist in the pons, medulla or spinal cord is proven by the experiment[32] of injecting tetra-hydro-beta-naphthylamine per jugular. Now this

[32] Ott. *Medical Bulletin.* 1898 and 1907.

agent is a powerful means of increasing the temperature to a high degree, but if you cut behind the tuber cinereum in a transverse direction, the drug is powerless to produce any rise of temperature.

Dana observed a child with an absence of the cerebrum, thalamus and cerebellum, in which the temperature was normal. Here the tuber cinereum, vaso-motor, respiratory and sweat centers took on the act of thermo-regulation. But I doubt if careful thermometric observations were made at different parts of the day in this case, as normal infants have a poor regulation of temperature. A premature infant of 6 months and 5 days had a temperature between 94° to 95°.

Sternberg and Latzow [33] report a case of hemicephalus in which the central nervous system existed only as far as the locus cœruleus, and there was marked insufficiency of heat regulation.

[33] Bechterew. "Nervencentra." Vol. II, p. 1198.

CORTICAL THERMOTAXIC CENTERS

Thermo-inhibitory Centers. Eulenburg and Landois located one in the dog at the cruciate sulcus. Prof. H. C. Wood (Senior) showed that its excision was followed by increased production of heat.

I have also located a center, which is called the sylvian, at the posterior part of the cortex. The existence of this center has been confirmed by Dr. W. Hale White, in the cat. He has also shown in a man that a shot from a pistol, injuring the anterior extremity of the middle lobe of the brain and also the third frontal convolution, caused a rise of temperature, 104.4° F. Roughly, this would correspond to the cruciate of the dog.

Page also reported a similar case of depressed fracture of the skull, in man, which injured the posterior part of the temporo-sphenoidal lobe. This roughly corresponds to the sylvian.

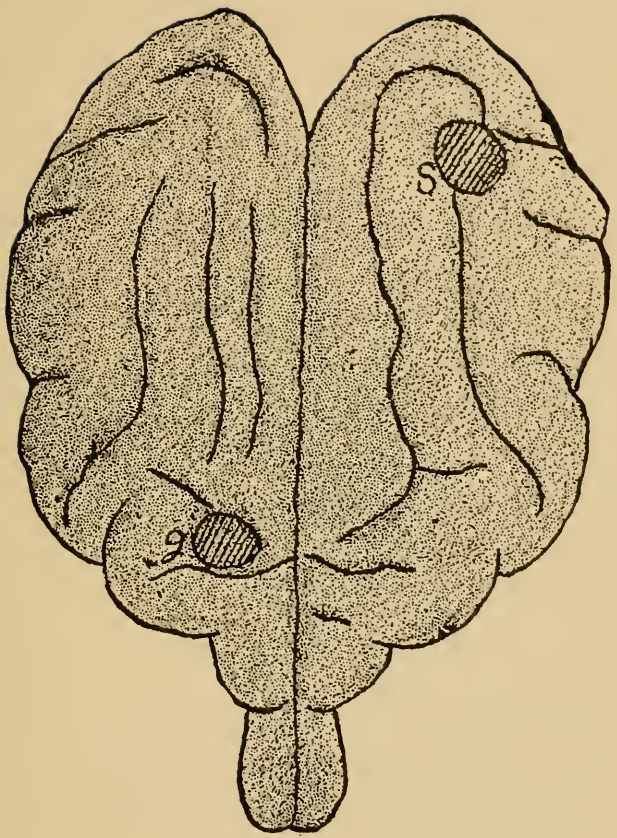

FIG. 2.
Thermo-inhibitory centers in cat's brain. S, sylvian C, cruciate.

The following résumé expresses my views of the thermotaxic centers.

The thermotaxic centers may be classified as follows:

Thermotaxic
- Thermogenic-tuber cinereum and corpus striatum.
- Minor thermogenic centers in spinal cord.
- Thermo-inhibitory, cruciate and sylvian.
- Thermolytic, polypnœic in tuber cinereum.
- Vaso-motor and sudorific.

THERMOTAXIC NERVES

A thermotaxic nerve may include thermogenic, thermolytic and afferent nerves connected with the thermogenic centers in the tuber cinereum and corpus striatum, which are concerned with heat regulation.

Boeke,[34] Botezat[35] and De Boer[36] have

[34] Boeke. "Anatom. Anzeiger." 1913. B. 44.
[35] Botezat. "Anatom. Anzeiger." 1910. B. 35.
[36] De Boer. "Fol. Neurolog." 1913. Band 7. S. 1.

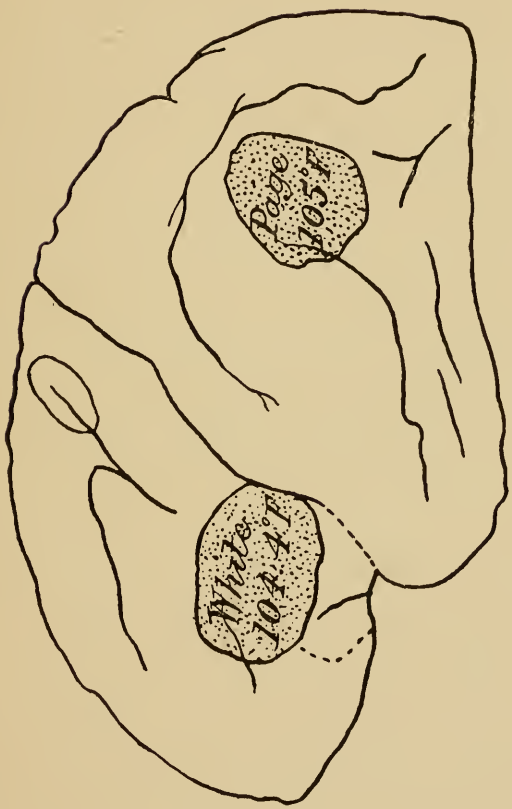

Fig. 3.
Great rises of temperature after injury to brain of man.

shown that every muscle fiber is supplied with sympathetic nerves. Hence they may contain heat regulating fibers.

There are some reasons to believe that they run in the vagus, for immediately after section of the vagi heat production falls. There are reasons to believe that they also run in the sympathetic nervous system, and possibly in the splanchnics which would cause more adrenalin and more mobilization of glycogen and more glucose, which being consumed would generate more heat.

EFFECT OF SECTION OF VAGI UPON THE TEMPERATURE, HEAT PRODUCTION AND HEAT DISSIPATION

I [37] have studied the effect of vagal section and found that the temperature generally fell immediately and that heat production and heat dissipation also usually were diminished.

[37] Ott. *Medical Bulletin.* 1895.

Sinelnikow [38] found, after section of the spinal cord between the fourth and fifth lumbar vertebrae or in the dorsal region to the seventh dorsal vertebra, puncture into the corpus striatum caused a rise of temperature. But when he cut out the action of large bundles of muscles by resection of the motor nerves the puncture produced less rise of temperature. Often the temperature rose more in animals with extensive paralysis than in animals able to move well. Hence, he infers that the puncture produces hyper-thermia but not through the muscular nerves. When he cut the spinal cord between the second and third dorsal vertebrae, the puncture was without effect. Here the visceral glands are in great part removed from the action of the thermogenic center in the corpus striatum. If then it is the visceral glands which are the chief source of heat, it becomes probable that several of the ther-

[38] *Archiv. f. Physiologie.* 1910. P. 278.

motaxic nerves run in the sympathetic nerves.

Hirsch and Rolly came to the conclusion that of the visceral glands, the liver was most important in the production of heat. Now the cells of the liver are supplied by the splanchnics, and probably they contain thermogenic fibers.

Schultze [39] cut the vagus and splanchnics on both sides and arrived at the conclusion that destruction of the nervous connections between the brain and the large abdominal glands does not prevent the appearance of hyperthermia after a puncture in the corpus striatum. He infers that the hyperthermia is at least not exclusively produced by the liver and pancreas.

These experiments show that the vagi and splanchnics are not the only paths for thermotaxic fibers, that others also descend in the pons, medulla and the lateral col-

[39] *Archiv. f. Exp. Pathol. u. Pharmak.* Band 43, p. 190.

umns of the spinal cord to the muscles and remaining viscera.

Ito [40] states that the warmest place in the body of the rabbit, after puncture, is in the duodenum, even when the animal has been without food for several days.

G. Hirsch and Rolly [41] found, after curarization, a marked hyperthermia in rabbits after puncture of the brain.

Streerath [42] found that small doses of strychnia caused the puncture to produce a higher temperature.

All these thermotaxic and thermolytic centers stand in a reflex relation to the skin and visceral nerves, probably those of the hot and cold spots, in the skin and similar nerves in the viscera.

Freund and E. Gräfe [43] made experi-

[40] Ito. *Zeitschrift f. Biologie.* 1889. Band 37.

[41] Hirsch u. Rolly. *Deutsches Archiv. f. Klin. Med.* Band 75, p. 307. 1903.

[42] Streerath. *Archiv. f. Physiologie.* 1910. P. 295.

[43] Freund and Gräfe. *Archiv. f. Exp. Path. u. Pharmakol.* Band 70, page 135. 1912.

ments upon rabbits, cutting the spinal cord at different levels and studying the gaseous exchanges. After section of the dorsal cord the physical regulation of temperature was interfered with and the heat production was increased. In section of the cervical cord at 7th cervical, the heat production was normal, but the physical and chemical regulation of temperature was disturbed.

By physical regulation is meant vasomotor changes and the evaporation of sweat and the water from the lungs. By chemical regulation is understood a reflex from the skin producing increased heat production, increased combustion of Rubner.

Frank and Voit [44] have shown by complete paralysis of the body in curarization, that the chemical regulation of the body heat is not lost.

[44] Frank and Voit. *Zeitschrift f. Biologie.* Band 24. N. D.

Dr. Robert Meade Smith and Dr. Lukjanow,[45] in Ludwig's laboratory, have studied in detail the fatigue of the thermogenic function in muscle, and also the law of recovery, with and without blood supply. Each mechanism of work and production of heat had its own laws as regards,—

(1) the influence of external conditions;
(2) the influence of fatigue;
(3) the influence of exhaustion;
(4) the influence of temperature, and
(5) the effect of rest and of circulating blood.

As Donald MacAlister [46] has stated, the contractile material in muscle is not the same as the thermogenic. The thermogenic is exhausted sooner than the contractile. Both can be upbuilt again by the circulating blood, but the contractile in some cases sooner than the thermogenic. Both

[45] Du Bois.-Reymond's Archiv. 1880.
[46] "Nature of Fever." 1887.

metabolisms are affected by cold, but the thermogenic much sooner and much more intensely than the contractile. There is no fixed relation between the laws of contraction and thermogenesis.

Freund and Schlagintweit [47] found as a result of experiments upon rabbits under curarin, that the chemical regulation can functionate without motor innervation of the muscles. Their experiments confirm those of Sinelnikow's, that during curarization the puncture into the thermogenic center elevates the temperature. Infection could not produce fever, but sodium chloride could generate it.

Freund [48] after section of vagi on the esophagus beneath the diaphragm in rabbits did not find the animals quite warm—their temperature stood at the lowest normal level. The animals were kept in a

[47] Freund and Schlagintweit. *Archiv. f. Exp. Pathologie u. Pharmak.* Band 71. Heft 3 and 4. P. 258.

[48] Freund. *Archiv. f. Exp. Pathol. u. Pharmakol.* Band 72, p. 295.

warm room, and the shaving of the abdomen may have been one of the causes of low temperature. After longer observation he saw no disturbance of heat regulation. The animals resisted cold and heat by their temperature regulation. The same was true when he cut the vagi in the neck and he doubts any inhibitory influence of vagi on temperature, as held by Stefani and Pari and also by Tscheschkow. Fever could also be produced with a solution of sodium chloride when the vagi were cut.

If the vagi and splanchnics are cut the results are similar; the animals can also become feverish after injection of sodium chloride solution. He saw no marked action by vagi on chemical regulation. Section of both vagi beneath the diaphragm, combined with the high dorsal cord section (above the 6th segment), had an effect similar to that of the dorsal cord section combined with extirpation of both stellate

ganglia, or to that of the dorsal cord section combined with the cutting of the 8th cervical and 1st dorsal root. The animal had no heat regulation with cold or heat, just as after section of the cervical cord. After these combined sections experimental fever could not be produced.

He finds it difficult to see an antagonism between the sympathetic and para-sympathetic system in heat phenomena. He states that heat regulation is in some way dependent on the abdominal organs.

Ott and Scott have also made a series of experiments upon rabbits, dividing both the right vagus and right sympathetic. The cervical sympathetic was also excised from the clavicle to the superior cervical ganglion. The temperature was taken in each axilla and in the rectum at the same hour, at intervals of about two days for a month. It was always found that the temperature of the right axilla was from 0.46° F. to 0.8° F. higher than that

of the left. Now how is the rise of temperature in these experiments explained? Temperature is maintained by the relation between thermogenesis and thermolysis. In section of the vagus and sympathetic we have destroyed heat regulation. The question arises, how has this been done? Have we cut vasomotor fibers, thus producing an increased flow of blood, which would cause rise of temperature? Or have we cut an afferent nerve of the tuber cinereum, the chief regulating center, which cannot through its efferent nerves in the vagus and sympathetic control heat regulation in the right anterior extremity. If, however, we take those experiments in conjunction with those of Freund, Strassmann and Gräfe where a section of the vagi beneath the diaphragm combined with section of the spinal cord about the upper level of the dorsal region destroyed chemical regulation, then we should infer that we have cut some of the

heat regulating fibers coming from the tuber cinereum.

Freund [49] divided the upper half of the cord in the dorsal region of the rabbit and found that heat regulation was destroyed. He then punctured the corpus striatum and the thalami. He found that section of the cord up to 2nd dorsal did not hinder the hyperthermia of heat puncture. When the animals become poikilothermal, then even heat punctures were without effect.

Freund and Marchand [50] found that removal of the adrenals caused a marked fall of temperature and a diminution of sugar in the blood.

Eimden, Lüthje and Liefman [51] have shown that in the dog with a low external temperature, the quantity of sugar in the

[49] Freund. *Archiv. f. Exp. Pathol. u. Pharmakol.* Band 72, page 304.

[50] Freund and Marchand. *Archiv. f. Exp. Pathol. u. Pharmakol.* Band 72, page 56.

[51] Eimden. *Lüthje u. Liefman. Hofmeister Beiträge,* 1907. B. 10.

blood is regularly considerably higher; and Silberstein [52] has shown on dogs that there is a very close relation between the quantity of sugar in the blood, the external temperature and the body temperature. In fever, as a rule, there is an increase in the quantity of sugar in the blood increases.

Freund and Schlagintweit [53] found that section of the dorsal cord below the 5th segment leaves the sugar puncture active, but if you cut above it there is neither glycosuria nor hyperglycaemia after the sugar puncture or injection of diuretin, whilst adrenalin produces a high hyperglycaemia. The section of the dorsal cord up to its highest segment leaves chemical regulation intact, which is seen in part from the rise of temperature after administration of diuretin and adrenalin. The central influence upon the metabolism of the carbo-

[52] Silberstein. "Warmeregulation u. Zuckerstoffwechsel." *Kong f. inn. Med.* Wiesbaden. 1913.

[53] Freund and Schlagintweit. *Archiv. f. Exp. Path. u. Pharmakol.* Band 76, page 303.

hydrates by chemical regulation is excluded, since the section of the splanchnics, as well as section of the dorsal cord above the 6th segment prevent the sugar puncture effect without disturbing heat regulation.

Nebelthan [54] found that section of the spinal cord in the rabbit between the 6th and 7th cervical vertebrae produced a fall of temperature and that infection with erysipelas of the pig had no influence on temperature or heat production. Here the toxines of fever act upon the heat regulation centers, but their thermotaxic fibers, in great part, have been cut off.

If the mid-brain is severed from the medulla, no fever can be produced, according to Sawadowsky.[55]

That thermotaxic fibers are concerned in

[54] Nebelthan. *Zeitschrift f. Biologie.* 1899. XXI, p. 353.

[55] Sawadowsky. *Centralblatt f. Med. Wissenschaft.* 1888. Band 26, p. 161.

chemical regulation of heat is rendered probable by the fact that section at the 7th cervical prevents a chemical regulation. If they were only concerned with augmenting or decreasing the activity of the ponto-bulbar centers then chemical regulation should continue. It is very probable that about the 7th cervical and in the mid-brain fibers run which are concerned in thermotaxis. Their pathway is probably the sympathetic and the vagus, whilst the cord fibers go to the muscles, and others enter the sympathetic ganglia and go to the cells of the viscera.

That fibers may go from the tuber to the thermolytic centers is very probable, for in the tuber is a vaso-tonic, and a polypnœic center and fibers may extend to the sudorific centers. This is the heat dissipation apparatus, or physical regulation of heat. But there is a heat producing apparatus also innervating the muscles through the

motor nerves and the viscera by the sympathetic system. This is the chemical regulation of heat.

I see no reason to assume, as some have done, that thermotaxic nerves do not run mainly in the nerves of the cerebro-spinal system to the muscles, but rather in the sympathetic. Certain fibers concerned with the production of heat can exist in motor nerves whether you hold that heat puncture can succeed or not in a curarized animal.

LECTURE II

LECTURE II

GENTLEMEN:—To-day I shall take up heat dissipation or thermolysis.

THERMOLYSIS

This is carried on by the polypnœic center in the tuber cinereum, the vaso-motor center, and the sudorific centers. In 1891, I [1] located the polypnœic center in the tuber cinereum which drives the respiration center to increased activity and thus throws off more water from the lungs.

Nicolaides of Athens [2] has made several experiments on polypnœa, and in 1910 located its center in the corpora striata. I

[1] "Fever; Thermotaxis and Calorimetry of Malarial Fever." 1889. E. D. Vogel, Easton, Pa. Also "Modern Antipyretics." 2nd edition. 1892. E. D. Vogel, Easton, Pa.

[2] Nicolaides u. Dontas. *Archiv. f. Physiol.* 1911. H. 3 u. 4. 249.

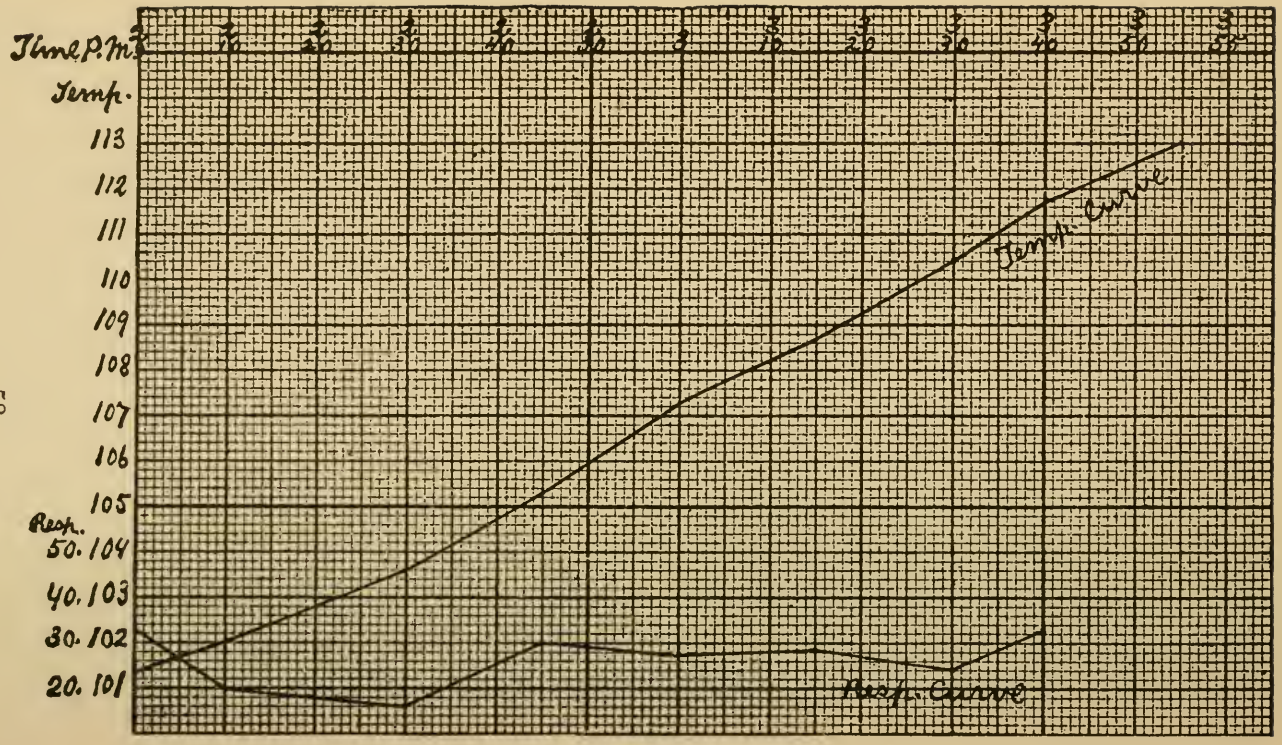

FIG. 4.

Effect of external heat upon respiration when corpo ra striata and tuber cinereum are removed.

have frequently cut away the corpora striata and obtained polypnœa. The center is localized, not in the corpora striata, but in the tuber cinereum. His statement, that there is no polypnœa without a thermogenic center, I can fully confirm, but the polypnœic center is in the tuber, while the thermogenic centers are in the tuber and the corpus striatum and of these the tuber is the governing thermogenic center.

Fig. 4. Shows the effect upon rabbit when the corpora striata and tuber cinereum are removed. As is seen, the respirations decrease instead of increasing, but increase somewhat at the temperature of 105° F., then remain about the same in number until about 110° F., when they again increase, but the rate never rose above the normal rate before heat was applied.

Fig. 5. Shows the effect of a weak faradic current applied to the tuber cinereum. When the base of the brain

was raised at its anterior part, the carotids being ligated during the elevation of the brain, and before the electric irritation they were removed. As is seen, there is a great increase in the rate of respiration.

Fig. 6. Shows the arrest of respiration when a single electric shock was sent through the tuber, with arrest of the thorax in a state of expiration. The curves are to be read from right to left.

Fig. 7. Shows the rate of respiration and the temperature curve in the normal rabbit.

That a polypnœic center exists in man is well supported by a case of Dr. Janeway's. He reports a hotel-keeper who in the fall of 1889 was thrown from the platform of an electric car, striking the pavement with his shoulders and the back of the head. In consequence of this fall, he remained unconscious ten days, and, when he recovered consciousness, found that he was breathing, as he expresses it, "like a

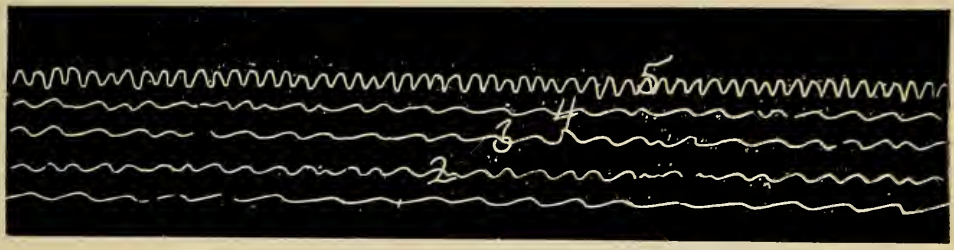

FIG. 5.
This shows the effect of a weak faradic current to the tuber upon the rate of respiration.

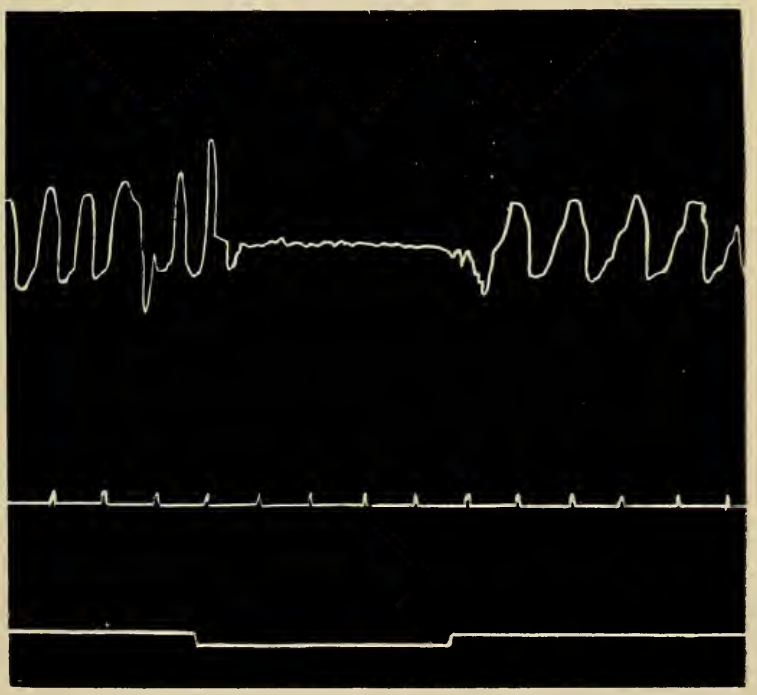

FIG. 6.
This shows the effect of a single electric shock to the tuber causing expiratory arrest.

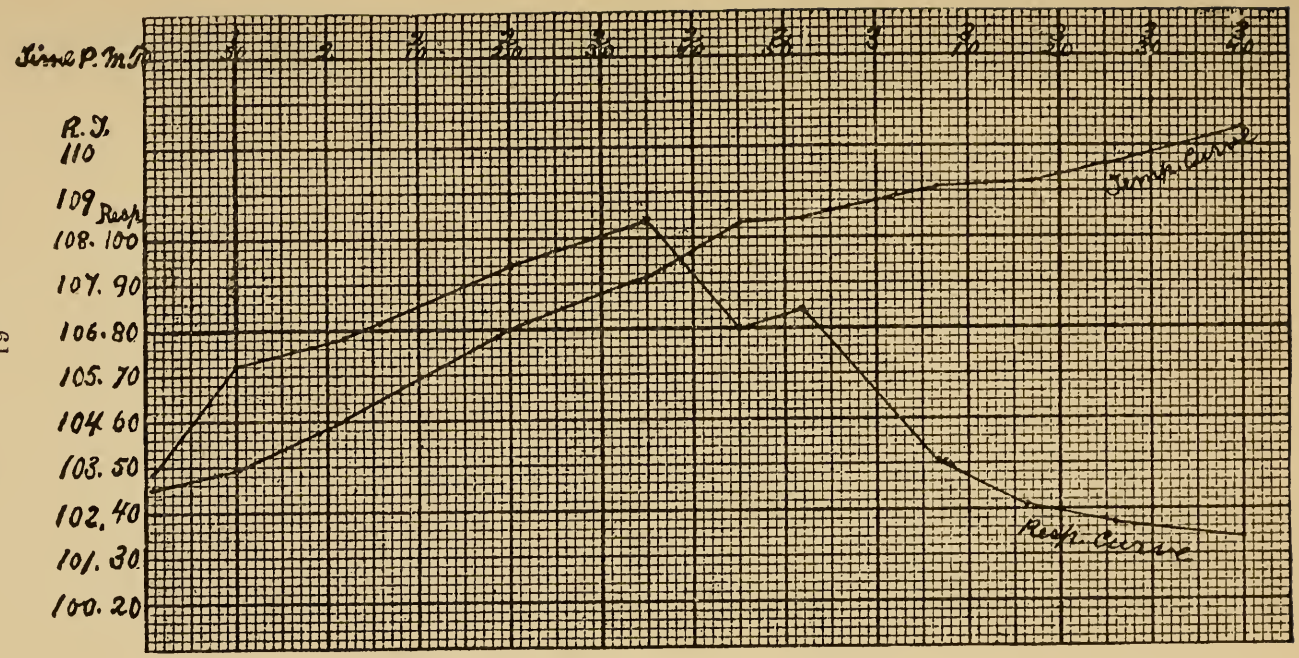

FIG. 7.

Effect of external heat upon a normal rabbit as regards the respiration.

steam engine at high pressure.'' He has breathed rapidly ever since, and in 1892—in February—the rate was 152 per minute. Otherwise he was in good health; the heart, lungs and other organs were healthy. He had a tracheitis due to the rapid respiration. This case turned out to be hysterical, although the functional trouble must have been connected with the tuber, for no one could voluntarily keep up so rapid a rate.

VASO-TONIC ACTION OF TUBER CINEREUM

There are also reasons to believe that the tuber has vaso-tonic activity, that is, gives tonus to the vaso-motor center.

Fig. 8. Shows the effect of puncture of the tuber. The arrow represents the time of the lesion, the dotted line the pulse, and the continuous line the arterial tension. The tying of the animal did not cause this fall, as the effect of detention does not ensue in the first hour, which was about the time the observation was continued. The

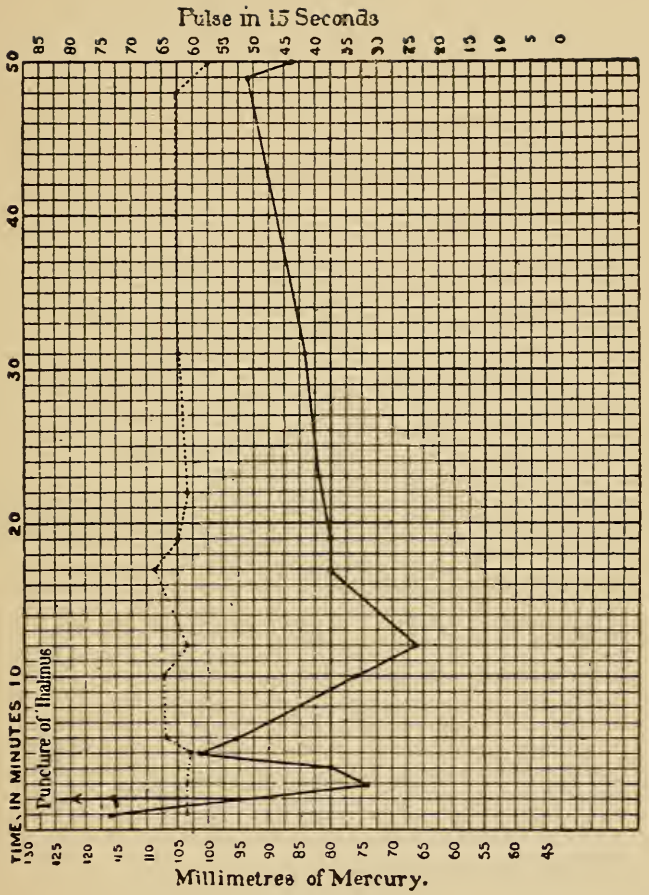

FIG. 8.

Effect of puncture of tuber cinereum upon blood pressure.

rate or the depth of the respirations was not perceptibly altered and did not influence the arterial tension.

This fall ensued invariably in six experiments. These observations left no doubt in my mind that vaso-tonic centers existed in the tuber cinereum.

SUDORIFIC SECRETION

The sudorific glands are under the control of the sweat centers in the spinal cord, whose fibers, I have shown, run down the lateral columns of the cord. The evaporation of water from the skin carries away considerable heat. It is stated that a man who had no sweat glands by hard work sent his temperature up to 40-41° C. and his respirations became rapid. Dogs who have no sweat glands cool themselves off by polypnœa, which carries off the water by the lungs instead of by the skin. The evaporation of a liter of water abstracts from the body 580 calories. A man will

lose daily about 930 calories by evaporation (about 400 calories from the water of the lungs and about 530 by evaporation of water from the skin).

Four-fifths of heat dissipation is through the skin, and the quantity of heat dissipated is proportional to the surface of the skin. Rubner measured the superficial area of the body and calculated the metabolism per square meter of surface, which he calls the "surface area law." In adults, resting, Ekholm found it to be 44 calories per square meter of surface per hour. Hence the metabolism of an animal varies approximately as its surface, and not as its mass. The relation of surface area to weight is much larger in the child than in the adult, and the heat production is proportionately larger. The relation of surface radiation to the development of fever explains the great liability of a child to fever. Disturbance in radiation from his large surface must disproportionately

influence the body temperature when compared with the relations in adults. Consequently a child becomes feverish very easily, and also becomes chilled very easily. Also the heat regulation centers are not so well regulated as in adults, hence chills and fever follow each other rapidly in children.

Heat regulation by the heat centers, mainly the tuber cinereum and less by the corpus striatum, is also weakened in sleep; hence the temperature falls from this cause and lessened production of heat on account of the muscular inactivity. Heat regulation in fever is also weakened, for cold applications have a much more marked effect in reducing temperature than they do in health.

Dr. Eugene F. DuBois, with a Benedict calorimeter, found in normal controls in man an average production of 34.4 calories per hour per square meter of the body surface.

Dr. Eugene F. DuBois of the Russell Sage Institute of Pathology, in Bellevue Hospital, N. Y., found with the Benedict respiration calorimeter that in typhoid fever the heat production might rise from 100 to 160 per cent. of the normal. He also found that at this stage there was little or no specific dynamic action manifested by protein or carbo-hydrates, that is to say, the taking of food, even in large quantities, did not increase the amount of heat produced. In exophthalmic goiter the total metabolism might rise as high as 192 per cent. of the normal and in cretinism it might be as low as 75 per cent. In all the various diseases studied the methods of direct and indirect calorimetry agreed closely.

INTERNAL SECRETIONS AND TEMPERATURE

In Basedow's disease heat production is increased, probably due to excessive heat dissipation, as the heart is weakened, the

arterioles are dilated, and the blood accumulating there gives off a considerable quantity of heat.

Boldyreff found after removal of the whole thyroid apparatus in cats and dogs that there was a loss of heat regulation. After elevation of temperature clonic convulsions ensued. After application of cold the temperature fell and the convulsions ceased. (Boldyreff. Pflueger's Archiv. Band 154, page 470.)

O. Loewi and Weselko[3] found no influence on temperature after extirpation of the thyroid in rabbits. Boldyreff found after extirpation of the whole thyroid apparatus in cats and dogs that it was very defective. They found that the heat puncture in thyroidectomized animals was always followed by a fall of temperature in the first hour instead of a rise as in normal

[3] Loewi u. Weselko. *Zentralblatt f. Physiologie.* 1914. No. 4, page 197.

animals. Then it rose at best only 1.3°, whilst in normal animals it rose 2.5° to 3°. Whilst in normal animals sugar metabolism by the heart at the temperature increase was greatly increased, but in thyroidectomized animals with puncture fever, it was the same as in animals with thyroidectomy alone.

In cretins the temperature is subnormal as in myxœdema, and thyroid extract when administered raises the temperature.

Infundibulin (pituitrin) (hypophysin of Fuehner), when injected, elevates the temperature. Cushing found that when the pituitary was removed and the temperature fell, an injection of the anterior part elevated the temperature 2-4° C. In conjunction with Dr. Scott I have seen the temperature fall to 94° F. after destruction of the pars anterior in a monkey. Ott and Scott found that large doses of the parathyroid lowered the temperature.

G. Liljestrand and K. Frumerie [4] found the normal variations of temperature in fasting rabbits are much smaller than in animals with the usual nourishment. After splanchnicotomy on both sides we have an elevation of temperature. The heat puncture in the corpus striatum succeeds well —a confirmation of the observations of Schultze and Elias. After extirpation of the solar plexus and the myenteric plexus in rabbit, the heat puncture is as effective as before; there is also some diarrhœa. After partial extirpation of the adrenals the effect of the heat puncture is weakened, —the more so, the greater the amount of extirpation. After complete removal of the adrenals the heat puncture does not act. After extirpation of the adrenals in rabbits there is often a diarrhœa.

Doeblin and Fleischman also removed the adrenals in three rabbits. In two the

[4] *Skandinavisches Archiv. fur Physiologie.* Band 130. 4, 5 and 6 Heft. P. 320. 1914.

temperature fell after the heat puncture. In the third animal the temperature rose, but the presence of aberrant adrenal tissue was not excluded.

In two rabbits the heat puncture was active when the adrenal was separated from the central nervous system. After extirpation of the solar plexus and myenteric plexus in the rabbit the heat puncture was active.

But the Swedish observers, Liljestrand and Frumerie, made many more experiments than Doeblin and Fleischman, and their results are to be accepted as the truth about the extirpation of adrenals preventing a rise of temperature after puncture of corpus striatum.

Ott and Scott [5] found in the rabbit that the repeated injection subcutaneously of 5 drops of adrenalin elevated the temperature from 103° F to 106.6° F., a rise of 3.6°. This was not due to more oxygen entering

[5] Ott and Scott. *Medical Bulletin.* 1907.

the lungs, as Gad's aeroplethysmograph showed that it reduced the volume of air entering the lungs. We infer it stimulates the thermogenic centers, because after cutting off the corpus striatum and the tuber, adrenalin did not in some cases cause any rise at all, the rectal temperature remaining the same. This rise of temperature was not due to diminished dissipation by vaso-constriction, as the temperature kept rising an hour and a half after the last injection of adrenalin solution.

The fact that heat puncture does not succeed when the adrenals are removed lends support to the view advanced by Ott and Scott, that adrenalin is a stimulant of the thermogenic centers, as there is no rise of temperature by adrenalin injections after removal of the tuber cinereum. It is quite probable that adrenalin is needed to sensitize the endings of the thermogenic nerves, the receptive substance of cells, so that the thermogenic centers can act.

Crile[6] has shown that there is an interdependence between the brain and the adrenals, that the brain cells (cerebellum in his experiments) show a quantitive relation to the work changes, that the brain is more dependent upon the adrenals than the adrenals upon the brain, that the brain cells have a strong affinity for adrenalin. Morphine lessens the amount of adrenalin in the brain cells. After excision of the adrenals there is a progressive loss of muscular power and a diminution of the body temperature. Ott and Scott have shown that foreign proteids injected into the circulation increase the amount of adrenalin in the blood, which has been confirmed by Crile. The fact that albumoses and peptones produce an increase of adrenalin in the blood may be the true cause of the fever in this case. Crile states that iodine aggravates Graves' disease and here we

[6] Kinetic System. *New York State Journal of Medicine*, May, 1914. Page 232.

have an increased temperature. Iodothyrin and, according to Crile, thyroid extract in large doses also cause fever; and Ott and Scott have shown that iodothyrin, iodine and thyroid extract increase the amount of adrenalin in the blood, confirmed by Gley, as shown by the intestinal strip, which action of adrenalin on the intestine in causing it to stop all its peristaltic movements and relax was shown by Ott[7] in 1886. In myxœdema we have subnormal temperatures. In Addison's disease, where adrenalin is deficient, there is also a subnormal temperature. Morphine diminishes the temperature and according to Crile diminishes the amount of adrenalin in the blood, and this lack of adrenalin may be one of the causes of the decrease of temperature by morphine.

From all these facts I infer that adrenalin has a very potent activity in the in-

[7] *Medical Bulletin.* 1886.

crease of temperature when it is in excess in the blood.

IS FEVER BENEFICIAL?

Crile holds that the fever may be so fierce in the destruction of bacteria that the body itself may undergo dissolution.

Adrenalin. Crile states that it causes hyperchromatism followed by chromatolysis and in over-doses destroys the cells of the cerebellum. When the adrenals are excised the Nissl substance disappears in a progressive manner up to death. Adrenalin excites the brain and causes the brain to convert latent energy into heat and motion.

Morphine. Crile found that under large doses of morphine the changes due to toxin of the brain cells were largely prevented. Thyroid and iodine have the same effect as infection and muscular exertion in the production of fever and of brain cell

changes. This is evidence, according to Crile, that certain constitutents of the brain cells are conserved in the work performed by the brain in the production of fever.

Fear causes fever in animals and Cannon has shown that it gives rise to the production of more adrenalin, which is one of the causes, here, of fever. Anxiety also causes fever, probably by excess of adrenalin in the blood. Crile observed an average rise of temperature, 1⅛° F., in a ward of children as a result of a Fourth of July celebration.

Crile found by the intestinal strip test that fear, rage, anaphylaxis after indolskatol, leucine and tyrosin and the toxins of diphtheria, of colon bacillus, toxins of streptococcus, staphylococcus, foreign proteids and strychnia increase the adrenalin in the blood. The test was negative after thyroid extract, anesthesia and trauma and after the injection of the juices

of the various organs of the same animal. Placental extract gave a positive reaction. After section of the splanchnics, the positive test by the above mentioned articles became negative. Deep morphinization prevented positive results by the foregoing adequate agents. In brief, all the agents which cause hyperchromatism and chromatolysis gave positive results for adrenalin. The one agent which protected the brain cells' Nissl substance was morphine. H-ion concentration test showed that all of the adequate stimuli giving a positive result in the intestinal strip test showed a diminution of the acidity of the blood from the adrenal vein. Alkalies cause histological changes in adrenals; acids do not. The adrenals activate the brain; the brain also activates the adrenals. Crile believes that the Nissl substance is a volatile, unstable combination of certain elements of the brain cells and adrenalin, because the brain deprived of ad-

renalin does not take the Nissl stain and the adrenals alone do not take the Nissl stain.

Morphine and nitrous oxide prevent the consumption of the Nissl substance, probably by preventing the oxidation of the brain. A combination of adrenalin, oxygen and certain brain cell constituents causes electric discharge that produces heat and motion. All of the adequate stimuli with the intestinal strip reaction, after prolonged insomnia which affected the brain and the adrenal tissues also produced identical histological changes in the liver cells. Hence Crile infers that the brain, adrenals and liver are mutually dependent upon one another for the conversion of latent into kinetic energy of heat and motion. In the rabbit insomnia of a hundred hours exhausted some of the rabbits and killed others. On post mortem and histological studies of all the tissues and organs of the body, there were marked

histological changes in only three organs —the liver, the brain and the adrenals. These bear the stress of life; the brain is the battery, the adrenals the oxidizer and the liver the gasoline tank and the muscles the furnace. The thyroid is the pace maker; it regulates the rate of discharge of energy.

Crile states that in Graves' disease we find an extraordinary degree of exaggeration of the whole action of the kinetic mechanism. Emotion, pain and infection produce an exaggeration of the conversion of energy. In acute Graves' disease the explosive conversion of latent energy into heat and motion is unequaled in any other disease. Feeding thyroid produces all the phenomena of Graves' disease except exophthalmus and the emotional facies. Excessive doses of iodine alone cause most of the symptoms of Graves' disease. Hence by normal, excessive, or subnormal secretion of the thyroid we produce nor-

mal, adynamic and an excessively dynamic state. Defective action by the organs in the kinetic chain causes loss of heat, loss of muscular and emotional action and the power of combating infection.

Overwhelming action of the kinetic system produces shock. The essential pathology of shock is identical with its cause. Crile states if the brain can not endure the strain we have neurasthenia; if the thyroid can not endure the strain we have enlargement of it or Graves' disease or colloid goitre. If the adrenals can not stand the strain we have cardio-vascular disease. If the liver can not endure the strain we have acidosis. If the liver's neutralizing effect is only partially lost, then the acidity may cause Bright's disease. Excessive activity of the kinetic system may cause glycosuria and diabetes. Emotional strain, pregnancy, stress of business or professional life are all activators of the kinetic system. Hence

we can understand how emotions, acute or chronic infections may cause either Graves' disease or cardio-vascular disease; how chronic intestinal stasis with the resultant absorption of toxins causes cardio-vascular disease, neurasthenia or goiter. It also affords an explanation of phenomena of shock, whatever the cause,—toxins, infections or foreign proteids, anaphylaxis, psychic stimuli or a surgical operation. The idea of the kinetic system has made possible the shockless operation, it has explained the cause and treatment of Graves' disease and the control of shock and acute infection by overwhelming morphinization.

HYPERTHERMIA

Pathologists for more than a hundred years have held that hyperthermia in fever was due to an increased production of heat. Virchow [8] by a study of the metabolism in fevers proved a greater intensity

[8] Virchow. "Path. u. Ther." 1, 1854.

than in normal conditions, and that it was the cause of the hyperthermia.

Traube [9] was the first to put forth the theory that hyperthermia was due to decreased dissipation of heat from constriction of the arterioles due to the action of the toxines, and not to an increased production of heat. But Tscheschichin, Auerbach, Wachsmuth combatted this view of Traube's.

According to Liebermeister [10] the hyperthermia is due, partly to an increased production of heat, but especially to a change in the heat regulation apparatus. Leyden [11] also supported Liebermeister in this view.

Senator [12] then made some experiments and supported Traube in his view that the

[9] Traube. "Beitrage z. Chem. Physiol. u. Pathol." 2 and 3. *Allg. Med. Centralztg.* 1863–1864.

[10] Handb. d. "Pathol. u. Ther. des Fiebers." Leipzig, 1875.

[11] Leyden. *Deutsch. Archiv. f. Klin. Med.* 536. 1869.

[12] "Untersuch ueber den fieberhaften Prozess." 1873.

most important factor in hyperthermia was the retention of heat, especially caused by the tetanic contraction of the peripheral vessels. Senator, however, believed that there was also an exaggeration of heat production, due to an increase in the combustion of the proteins, whilst the combustion of the carbohydrates and fats did not change much.

Then we have the theory of Murri [13] that fever is not produced by retention of heat but by an increase of thermogenesis, due to a direct action of pyretogenic substances upon the cells of the organism independent of the nervous system. These are the principal theories of the second half of the nineteenth century.

Babak [14] holds that the heat production in fever is slightly diminished. Such are the principal views of many observers, but

[13] Murri. "Del Potere regolatore della temperature animale." Firenze, 1873.

[14] Babak. "Ueber die Waermeregulation im Fieber." *Archiv. f. d. ges. Physiologie.* 102, 320. 1904.

the mass of testimony shows that there is an increased production of heat in fever, and afterwards that the heat regulation apparatus is reset at a higher figure, as Liebermeister taught.

Porcelli-Titone [15] has made experiments on rabbits with a water calorimeter. He produced fever with

(1) The nucleo-proteid of plague bacillus;

(2) Toxine of colon bacillus;

(3) Toxine of streptococcus;

(4) Nucleo-proteid of streptococcus;

(5) Nucleo-proteid of typhus bacillus;

(6) Toxine of diphtheria;

(7) 0.85 per cent. sodium chloride solution.

He injected these substances into a vein in the ear. In the cat he used the nucleo-proteid of the plague bacillus and toxine of colon bacillus, whilst in the dog he used

[15] Porcelli-Titone. "Biochemische zeitschrift." Band 58, page 365. 1914.

the streptococcus and the plague bacillus. He used an electric motor to run the agitator to mingle the water, a method first used in the Ott calorimeter, in 1892. The error of the instrument of Titone was 0.1 calorie. The error of Ott's little calorimeter for animals is 5.4 per cent. when tested by burning absolute alcohol.

Titone's results were as follows: The heat balance during the beginning of a fever is different, according to the pyretogenic agent. It depends not only on the fever producing agent but also upon the kind of animal. In rabbits there is a great increase of heat production by the action of nucleo-proteids, and typhus bacillus and a small increase by action of sodium chloride solution and the toxines of colon bacillus; no temperature changes ensued from the diphtheria toxine. The nucleo-proteid of streptococcus and still more the plague bacillus lowered thermogenesis.

In dogs the nucleo-proteid of plague

bacillus caused a slight increase in heat production, while the streptococcus produced a great increase.

In cats the nucleo-proteid of the plague bacillus lowered heat production, while the toxine of the colon bacillus caused a marked increase.

The estimations of the Co_2 eliminated confirmed the direct calorimetric data.

As hyperthermia can be called out when the heat production is diminished (at times 20%) and in other cases where the heat production is increased (but generally not beyond the physiological variations) it shows that there is no constant quantitive relation of heat production to the elevation of temperature. Hence Titone's hypothesis is that the greatest factor in the hyperthermia of fever is diminished heat dissipation. From these data it is probable, he states, that the pyretogenic agent calls up hyperthermia by an action upon the heat regulation mechanism for dissipation

of heat, and that this is independent of the action upon the thermogenic apparatus. He believes that his experiments showed that the different results obtained by various observers were due to different types of fever studied, and the different kinds of animals used.

As to the last mentioned view, *I* might state, in man we have an increase of gaseous exchange in fever (Leyden, Liebermeister, Regnar, Loewi, Kraus and Chvostek, Riethus), or a decrease of gaseous exchange (Wertheim, Grehant and Quinqaud, Riethus). While the majority of observers on man with a calorimeter found an increase of heat production (Liebermeister, Wahl, Hattwich, Chesnocoff, Leyden, Langlois), others found, like Traube, a diminished dissipation (C. Rosenthal, Maragliano, T. Rosenthal). Here the same animal was used, yet different results were obtained.

Temperature is the relation between

heat production and heat dissipation, and while high temperature is usually caused by increased production of heat, it can also be the result of a diminished production with a diminished dissipation, as I have found pretty frequently in my calorimetrical work.

The animal may start with a normal heat production and heat dissipation, and the regulation be set lower instead of higher to produce a high temperature. It is quite probable that these exceptional cases are explanatory of some of the discordant results, and not the variety of animal or the different toxines used, as held by Titone.

The amount of Co_2 follows heat production, according to Titone, and if so, the discordant results in gaseous exchanges can be explained in the manner just mentioned.

As to the afebrile causes of typhoid fever, the setting of the heat regulation

apparatus at a lower level explains them also.

HEAT PRODUCTION IN NORMAL AND HYPERTHERMIC CONDITIONS

Dr. Wm. A. Carter made a series of experiments upon rabbits, cats and dogs in my laboratory, showing the heat production and heat dissipation during twenty-four hours, the animal being in a state of hunger for three days. Out of twenty days the maximum heat production came at 7 A. M. three times, at 11 A. M. twice, at 3 P. M. five times, at 7 P. M. three times, at 11 P. M. four times and at 3 A.M. three times, or ten times during the day and ten times at night. In experiments in which the same animal was used the maximum and minimum of heat production did not appear twice at the same time. There was no diurnal rhythm of heat production and of heat dissipation. There was the usual diurnal rise of temperature in the evening

(7 P. M. to 11 P. M.) and the minimum morning temperature (7 A. M. to 11 A. M.), the same as has been found in man.

In another series of experiments Carter used hungry animals, and the cruciate center of Eulenburg and Landois was destroyed, which developed a hyperthermia. The results showed a much greater variation in temperature in the animal with hyperthermia when compared with the normal animal. Here it was found that heat production and temperature were entirely independent of each other. We give in Figs. 9 and 10 two composite curves showing the average heat production, heat dissipation and rectal temperature. The continuous line represents heat production, the dotted line heat dissipation, and the line below shows the rectal temperature.

PROF. WOOD'S EXPERIMENTS

The chief work on artificial fever in this country has been done upon dogs by Prof.

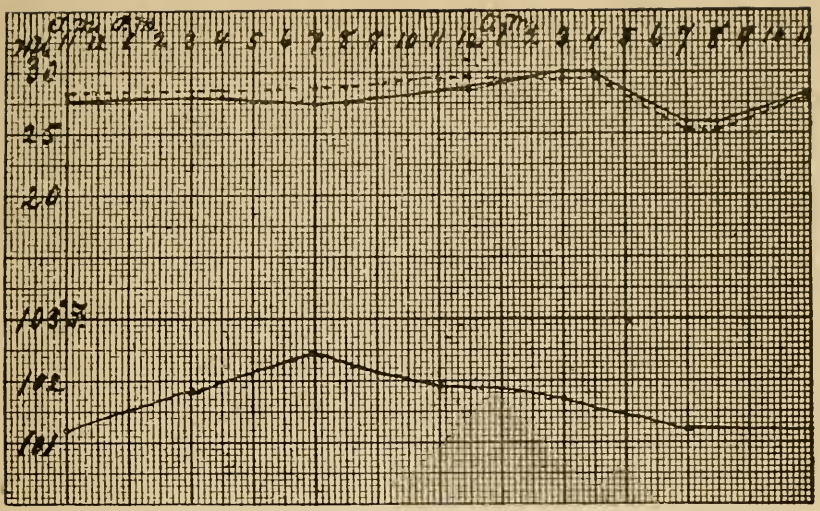

FIG. 9.

Composite curve showing the average of 20 experiments upon starved animals.

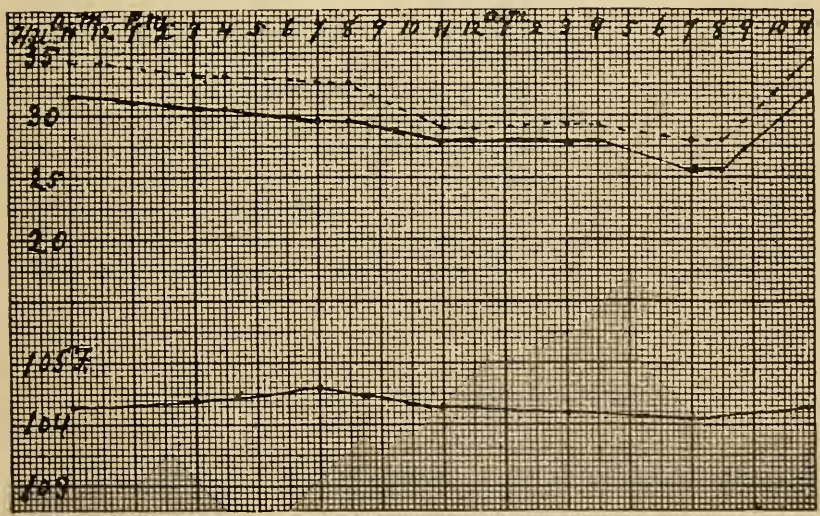

FIG. 10.

Composite curve showing the average of 12 experiments upon fevered animals.

H. C. Wood (Sr.) in his laboratory.[16] It was upon the heat production and heat dissipation in animals made feverish by the injection of putrid blood. He also studied pepsin fever in conjunction with Drs. Reichert and Hare.

Tabulation of Prof. Wood's results gives the following results:

+ means increased H. P., — decreased H. P., compared with the second day.

	H. P. 1st fever day.	H. P. 2d fever day.
Exp. 110	+ 26	+ 31
" 111	+ 2	+ 5
" 112	— 6	+ 8
" 113	— 3	+ 18
" 114		+ 37
" 116	+ 3	

An examination of Professor Wood's results show on the first fever day an increase of H. P. in three experiments, and

[16] Wood. "Fever," 1880. *Smithsonian Contributions to Knowledge.* No. 357. "Fever Thermotaxis and Calorimetry." 1889. E. D. Vogel, Easton, Pa.

a decrease of H. P. in two. On second fever day there is an increase in five experiments.

These increments are much greater than those found by me, and are partly due to observations made at dissimilar parts of the day without regard to the diurnal rhythm.

My experiments upon fever were made in 1889 upon rabbits and cats deprived of food for twelve hours before any observations were made. They were carried on for seventy-two hours.

The access of fever was studied during the first three hours and at intervals afterward. It showed that after injection per jugular of two drops of putrid blood, the heat production rises rapidly and becomes greatest some hours before the fever curve attains its height. At the same time the curve of H. D. is lagging behind the curve of H. P., although following it in its upward ascent. After a while the H. P.

curve falls temporarily beneath the curve of H. D. and the temperature curve falls. It will be seen normally and during the fever in the curve of H. P. that it exhibits fluctuations, a fact pointed out by Senator. The fluctuations of H. P. are greater in fever. I believe the fluctuations are due to the action of external agencies upon the thermotaxic, thermogenetic and thermolytic apparatus, which are playing at see-saw, at one time making H. P., greater than H. D., at another making H. D. greater than H. P.

In Exp. 1 there is an illustration of a high temperature, although H. P. and H. D. have fallen below normal of the hunger day or second day. In Exp. 4, we see that during three-fourths of the last fever day the temperature is below normal, and at the last observation H. P. is five units greater than those of same period on hunger day. The question arises how is Exp. 1 to be explained?

Dr. Donald MacAlister [17] has given the following explanation. Suppose a tall vessel containing water, the level of the water representing temperature. Let two pipes be connected with this vessel, one conveying water, the other carrying it off. Let the inlet and exit tubes be each provided with a stop-cock, and let the two stop-cocks be connected by a rigid link which insures that they always turn together and by the same amount. If to start with, the inflow and outflow are equal, then however I move the linked stop-cocks, the height of the water will be the same. Now remove the rigid link and connect the stop-cocks by a spiral spring. If now you move the inflow stop-cock so as to increase the flow, the outflow one will not at once follow, and, the balance being broken, the level of water will rise. But shortly the elasticity of the spring comes into activity, the outflow is

[17] "Fever Thermotaxis and Calorimetry." 1889. E. D. Vogel, Easton, Pa.

equal to the inflow and the rise will cease, but the new high level will be maintained. Every movement of either stop-cock will affect the level, which will fluctuate accordingly, but its height at any moment will not be an index of the amount of inflow at that moment. The inflow may be slight while the level is high. If now you substitute H. P. for inflow and H. D. for outflow, and the rigid link represents the healthy thermotaxic mechanism, then when this is weakened or relaxed or broken the steadiness of the normal level is impossible.

PROTEIN FEVER

Ott and Collmar [18] studied the effect of albumoses and peptones upon animals. We discovered, in 1887, that they produced fever. The albumoses and peptones were prepared from egg albumen by Professor

[18] Ott and Collmar. *Journal of Physiology*, Vol. VIII, p. 218. 1887.

Chittenden of Yale and were injected per jugular. We made experiments upon rabbits and found that both albumoses and peptones produced fever by an increased production of heat, but during the first hour the heat production is decreased by the peptones, whilst the albumoses increased it during the first hour. Both usually decreased heat dissipation during the first hour, which then rose with the increased production. Krehl and Matthes,[19] in 1895, confirmed these facts. Vaughn,[20] in 1909, demonstrated it also by the administration of foreign protein parenterally.

FEVER IN MAN

Calorimetry of Malarial Fever. In my experiments it was brought out for the first time that in septic fever the heat production and heat dissipation may be

[19] Krehl and Matthes. *Archiv. f. exp. Path. u. Pharm.* 1895, XXXV. 232.

[20] Vaughn. "Protein Split Products." P. 372. 1914.

diminished during the whole course of the fever. Usually septic fever in its initial stage is accompanied by an increased production of heat. Now it is easy to definitely settle the question as to the increase or decrease of heat production in fever, and I have studied the calorimetry of malarial paroxysms during the cold, hot, and sweating stages. The instrument which I have designed is constructed as follows:

It is composed of two cylinders of galvanized iron—one smaller than the other and enclosed with it (Fig. 11). The space in which the man lies upon a mattress is six feet long and two feet in diameter. Air is conveyed to him through the tube H (to which is attached at its inner end a coiled leaden tube through which the air enters the instrument), and traverses the whole length of the apparatus and enters the hollow tube of lead at P, and finally emerges at B, having given off its heat to the water between the two cylinders. The

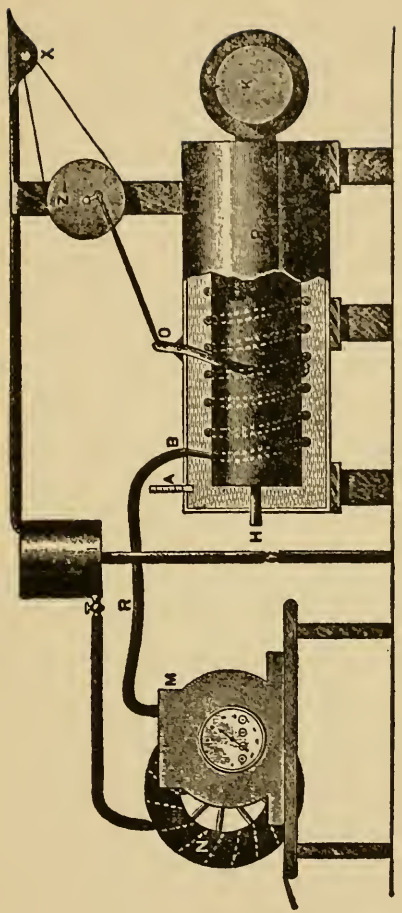

Fig. 11.
Ott's Calorimeter for man.

meter, M, is run by the water-wheel, N, which aspirates the water through the whole apparatus by means of a hose, R, connecting it with the lead tube at B. The space between the cylinders is filled with about four hundred and eighty-four pounds of water. This water is kept thoroughly mixed by means of the agitator, O, which has two arms. These arms are pushing the water back and forth thirty times a minute, the motion being caused by water running the motor, X, which, by means of the wheel, Z, and the eccentric, drives the agitator. The thermometer, A, gives the temperature of the water, and on account of the thorough mixing of the water by the agitator, gives the accurate record of the temperature of the water throughout the apparatus. The thermometer is pushed farther down than is represented in the figure; it usually lies aside of the tube H. The air-tube, B, also has a thermometer to denote the temperature of the air as it

is heated up by the man. The thermometer at B is graduated into tenths, while the thermometer at A is graduated into fiftieths, but they are so far apart that one one-hundredth of a degree Fahrenheit can be read. The temperature of the mouth was taken by a thermometer giving tenths, but I expect to use one so graduated that I can read fiftieths. The rectal temperature would have been preferable on account of accuracy. The bucket, I, receives the water from the motor, X, and so conveys it to the water-wheel, N, that it runs the meter as an aspirator. The meter is filled with water, and belongs to Voit's little respiration apparatus. The quantity of air aspired an hour is five to six thousand liters, which is sufficient for respiratory purposes. The instrument is made air-tight by means of the door, K, which is clamped by eight powerful iron clamps. The inner edge of the door is lined with rubber. The whole apparatus is enclosed

in over six inches of saw-dust, the door, K, having against it a saw-dust mattress. The interior of the instrument is lighted by an electric light of one-candle power, by which a paper can be read.

With these arrangements, excepting light, and a mattress inside the instrument I have tested the apparatus. As the apparatus necessary for the hydrogen test was not available, I used absolute alcohol. The different physicists who have burned a gramme of alcohol have obtained the following various numbers: Thus Rumford obtained 6,195; DuLong, 6,962; Andrews, 6,850; and Favre and Silbermann, 7,183.6. These numbers mean so many gramme-calories, and the number 7,183.6 is supposed to be the most accurate. In their experiments, in order to allow for the loss of heat due to radiation, a preliminary experiment was made with the body whose heat was sought, the only object of which was to ascertain approximately the increase of tem-

perature of the cooling water. If this increase be 10°, for example, the temperature of the water calorimeter was reduced one-half this number—that is to say, 5° below the temperature of the atmosphere. By this method the water of the calorimeter receives as much heat from the atmosphere during the first part of the experiment as it loses by radiation during the second part. This procedure is called Rumford's compensation. In the human calorimeter the air tube must be of considerable size for the air to enter, and necessarily permits of considerable loss of heat by the air constantly traversing the instrument. I have tested my calorimeter before and after the performance of the experiments.

All results by my calorimeter must have 15.5 per cent. added to them, that they may be accurate. In this paper I have made the percentage of error 16 per cent., as the mean of several experiments showed this to be the average error of the instrument.

The constancy of the error made the apparatus one of precision for scientific work.

In my experiments upon man the calculation was made in the same manner. The specific heat of the body was taken to be 0.83.

In estimating the moisture I used Voit's little respiration apparatus, taking the moisture of the air of the room and deducting it from the moisture of the air coming from the calorimeter. Now, according to Helmholtz, 1,000 grammes of water require 582 calories in evaporation from the lungs and skin.

The glass bulbs were filled partly with sulphuric acid, and weighed upon a delicate balance before and after the absorption of moisture from the air.

By placing a pulley outside the calorimeter and attaching to a leather rope a fourteen pound weight, the man within the instrument was able to exercise. The leather band entered one of the air holes

of the instrument. In this manner it was found: 1. That a man weighing one hundred and ninety-two pounds, during the afternoon produced 410 heat units per hour on an average and not 512 as calculated by oxidation changes and the amount of egesta. 2. Of the whole amount of heat dissipated, about 14 per cent. is thrown off by the lungs. 3. The elevation of about five tons an hour a foot high doubles the hourly heat production.

The study of the calorimetry of malarial fever has never been attempted, except by a study of the changes in the leg or arm. Langlois attempted by an air calorimeter to study the heat production in pneumonia of children, but the instrument is by its construction so inaccurate, that it will give only very gross changes.

The instrument used in the study of the malarial paroxysm is accurate in its workings as has been already detailed. Through the great kindness of Dr. J. F.

Berg, of Plainfield, N. J., I was able to study upon the person of Mr. W. W. Schenk, the first accurate calorimetry of malarial paroxysms. Mr. S—— was 5 feet 9½ inches in height, aged twenty-nine, a farmer, and the chill he had was the fourth one. During the course of this tertian intermittent fever, he was taking no medicine. He ate a very light breakfast at 7.30 A. M. At 8 A. M. his temperature was 98, at 9.30 A. M., 99.2, felt catching pains in the nape of the neck; at 10.18 A. M., he entered the calorimeter, temperature 100.1. While in the calorimeter he had chills running up and down his back, his hands felt cold, and he had a general sense of chilliness. Upon leaving the instrument, 11.18 A. M., his pulse was 84, temperature, 101.85; 10.35 A. M., thirsty, feels badly, looks pale, bones and head ache, has a pinched and anxious look; pulse 92. At 11.47 A. M., again entered the calorimeter, temperature, 101.4, left instrument at 12.48 P. M.,

temperature, 102.0; pulse, 112; complains of heat while in instrument, face flushed, hands moist. At 1.15 P. M. ate a fair dinner. At 1.40 P. M., pulse 84; temperature, 100.6; headache, face flushed, some perspiration. 2 P. M., temperature, 100.2, entered calorimeter; 3 P. M., left it, pulse, 84; inside of calorimeter moist from perspiration, he noted the musty odor for the first time in the instrument. 8 P. M., temperature, 98.2; feels quite good; had four movements of bowels, supposed to be due to water not accustomed to.

Second day.—7.30 A. M., ate a good breakfast, entered calorimeter at 9.53 A. M., temperature 99.0; left instrument at 10.53 A. M., temperature, 99⅖; pulse, 84; at 11.22 A. M., entered calorimeter, temperature, 99.25. At 12.22 P. M., left it, temperature, 99.25; had another movement of bowels, took a whisky before dining at 1 P. M.

At 1.35 P. M., again entered the calorimeter, temperature, 99.2; left it at 2.35

P. M., temperature, 99.7; pulse, 92; felt good, and left for home on Saturday.

On following Sunday had a light chill. No chills since. One week since the last chill he again entered the calorimeter for a test of his normal heat production. He was well, and ate heartily. On the previous day he was engaged in very laborious work.

By means of the electric light (which gives a very uniform heat) of one candle power, he was able to read the morning news while his heat production was being taken. It was found by burning absolute alcohol, that with the electric light, the error was 2.8 per cent. which was to be deducted from the amount of heat production registered by the calorimeter.

From a study of Fig. 12 it is found that during the initial stage or chill-period of a malarial paroxysm, the dissipation is not as great as at other times, and the heat production is enormously increased. After

the fever reached its height, the previous great rise of heat production was succeeded by a great fall, according to the law of compensation. Here high temperature is not an index of a correspondingly high production of heat.

In the stage of defervescence, heat dissipation is greatly increased and heat production does not regain its original height. It is only during the sweating stage that the excess of moisture comes over in the sulphuric acid bulbs on the fever-day. If the heat production on the chill day and on the succeeding day is compared with that of the normal day, it will be found to be on the chill-day 79.3 heat units in excess, and on the succeeding day 9.6 heat units in deficit. This is a much greater increase than that seen in the septic fever of animals.

These observations show how fever in man is originated, that is, usually heat production runs rapidly ahead of heat dissi-

pation, which is partly lessened, and the temperature is elevated. On the next day after the malarial paroxysm there was a slight fever, and the heat production on the average was lower than on the preceding day.

There is every reason to believe that in a continued fever this increase of heat production does not usually last many days, but that the fever continues because of an altered relation between heat production and heat dissipation, without regard to an increased or diminished heat production. These observations confirm a modified theory of Liebermeister's. The theory of Traube, that fever causes a vaso-motor spasm; that of Marey, that a vaso-paralysis exists; or the more recent view of Rosenthal, that of heat retention—all these theories contain only a germ of truth, that is, during the chill and fever there is a lessened dissipation of heat when compared with the sweating stage. Appended are

the calorimetrical results upon which Fig. 12 is founded.

"CHILL" DAY.

A. T. = Air temperature.

C. T. = Calorimeter temperature.

E. T. = Temperature of exit air tube.

M. T. = Temperature of mouth tube.

Litres = Amount of air aspirated through the calorimeter.

A. M.	A. T.	C. T.	E. T.	M. T.	Meter
10.18	73.3	67.70	20.6	101.1	Litres 51.37
11.18	72.8	68.38	21.1	101.85	Weight 138 9/50
		.68		.75	

H. D. = 369.1 H. P. = 569.8

A. M.	A. T.	C. T.	E. T.	M. T.	Meter
11.47	73.1	68.36	21	101.85	Litres 50.40
12.47	74.0	69.01	21.6	102.00	Weight 137 29/50
		+.65		.15	

H. D. = 354.0 H. P. = 371.1

P. M.					Meter
2	75.3	68.95	21.6	100.2	Litres 47.92
3	73.9	69.57	21.8	100.6	Weight 138 40/50
		+.62			

H. D. = 373.1 H. P. = 419.2

DAY AFTER THE CHILL.

A. M.	A. T.	C. T.	E. T.	M. T.	Meter	
9.53	73.7	69.14	21.2	99.0	Litres	54.53
10.53	75.3	69.69	22.2	99.4	Weight	136 40/50
		.55		.4		

H. D. = 355.4 H. P. = 400.8

A. M.	A. T.	C. T.	E. T.	M. T.	Meter	
11.22	74.3	69.68	21.8	99.25	Litres	51.50
12.22	75.2	70.29	22.2	99.25	Weight	136 31/50
		.61				

H. D. = 335.8 H. P. = 335.8

P. M.					Meter	
1.35	77.8	70.22	22.2	99.2	Litres	52.15
2.35	75.8	71.75	22.4	99.7	Weight	137 44/50
		.53		.5		

H. D. = 338.7 H. P. = 395.9

NORMAL DAY—ONE WEEK AFTER HE HAD A CHILL

A. M.	A. T.	C. T.	E. T.	M. T.	Meter	
11.06	71.0	65.60	19.0	98.05	Litres	52.51
12.06	72.2	66.20	20.2	98.85	Weight	138.58
		.60		.80		

H. D. = 373.8 H. P. = 414.0

P. M.	A. T.	C. T.	E. T.	M. T.	Meter	
12.24	72.2	66.16	20.0	98.85	Litres	50.04
1.24	72.0	67.78	20.4	98.85	Weight	138.44
		.62		0		

H. D. = 342.88 As no electric light, add 16% = 54.86
H. D. = 397.74
H. P. = 397.74 No moisture came over.

P. M.						
2.35	73.4	66.86	20.6	98.5	Litres	48.73
3.35	74.1	67.34	21.0	99.4	Weight	140.12
		.48		.9		

H. D. = 264.82 No electric light, add 16% = 42.37
H. D. = 307.19
H. P. = 411.19 No moisture came over.

Through the great kindness of Dr. F. G. Benedict of the Carnegie Nutrition Laboratory, I have obtained a translation of a paper [21] upon the heat phenomena in malarial fever, which confirms my researches

[21] A. A. Lichacheff and P. P. Avroroff. "Investigations of Gaseous and Heat exchange in Fevers. (Febris intermittens tertian.)" A separate reprint from volume V, parts 3 and 4. Reports of the Imperial Military Medical Academy. St. Petersburg. Printing office of M. Merusbera, Nevski prospect 8, 1902.

made ten years previous to theirs. As it is rather inaccessible to many of us I shall give you an abstract of considerable extent.

LECTURE III

LECTURE III

GENTLEMEN.—In this lecture I shall continue the study of malarial fever and the metabolism.

Their investigations were made with a water calorimeter of Professor Paschutin, and at the same time they measured the gaseous exchanges. (The calorimeter is described by Lichacheff. Heat production in a healthy person when in relative rest. Dissertation, St. Petersburg, 1893. A description of calorimeter of Paschutin.)

The calorimeter was oval in form, about 3 yards in length and the same in height, with a capacity for air of about 2.7 cubic meters. In this space is a metallic net instead of a floor, with a bed consisting of a rubber mattress and pillow inflated with air. For sitting a bench is placed in the

chamber and the person can make two to three steps. The chamber can be closed hermetically by two covers (one inside the other, in which are two glass windows). The ventilation is by a special suction air-pump, which is operated by a gas motor, and can suck out 150 liters of air in a minute. The ventilation was ordinarily 80 liters in a minute, or about 5 cubic meters of air an hour. The air entering the chamber was first deprived of Co_2 and water by absorption by potash and concentrated sulphuric acid. The air coming out of the chamber was conveyed through sulphuric acid and potash. There was an electric light in the chamber, of one candle power, and its heat estimated. The temperature of the apparatus ranged from 17-20 C.

For signaling purposes there was a bell and for talking a speaking tube which was divided by a thin impenetrable gauze or cover of natural rubber.

Before beginning the experiment, they

weighed the food, the jars of urine, feces, the linen wear, the clothes and bed of the sick one. The moisture of air in the apparatus was determined with the aid of a psychrometer. The patient was weighed and immediately placed in the apparatus. After closing the covers of the calorimeter, which required about half an hour, the ventilating air would be admitted into the chamber and the stirring of the water in the calorimeter was commenced for the purpose of reading an even temperature in the apparatus. However, the calorimeter determination would begin, not at once, but an hour or more later, with the object that during that time it would settle itself to the well-known more or less constant relationship between the temperature of the apparatus and the temperature of the surrounding moist conditions, which are to be observed in reaching a high degree of precision in the indications of the apparatus. In order to obtain the results as to the in-

tensity of heat production and exchange of matter during different moments of the fever attack, the test of the whole 24 hours was broken up into separate periods, each continuing 2 hours, thus we had 11 periods of 2 hours each. At the end of each period she would have a change of temperature during ¼ hour, and we would record the readings of all the thermometers of the apparatus (calorimeter, as well as under the skin, and that of the room). For a still more accurate observation we recorded the thermometers not only at the end of two hour periods, but also in the middle of it, that is, we would make records each hour, also the temperature of the patient (a woman during the fever attack) was measured each hour.

The patient, Anastasia Zarerski, was 17 years old, weighing 49.321 kilograms. The fever was a tertian intermittent. They made observations during the attack of fever on May 12 and May 14, and a third

series of observations during the time of absence of fever on May 18-19, that is, 4 days after the last fever attack. After May 15 and 16, she received quinine. Her maximum temperature was, at 6 P. M., 36.7° C., and minimum, at 11 P. M., 36° C. During the rest of the night and day the temperature kept within the limits of 36.2°-36.6°.

HEAT PRODUCTION

Heat production in the evening hours at the beginning of the observation stood at about 85 kilo-calories per hour, then it began to fall quite rapidly and by 5-7 in the morning it reached its minimum, which was about ½ the quantity of the evening figures—46 calories per hour. This considerable reduction of heat production within the organism coincided with the time of sleep of Miss Zarerski. During morning hours heat production would somewhat increase and stood at a height

of 70-65 calories per hour, and in the afternoon, from 3 to 5 P. M., it increased still more, up to 77 calories. Just as in the evening hours we observed a maximum of heat production, so we also had a maximum temperature in normal healthy men. She normally had 32 calories per kilo of weight.

HEAT LOSS

The absolute amount of heat loss was maximum 91 calories per hour from 7 to 9 in evening, minimum, 53 calories, from 5 to 7 in the morning. During the daytime heat loss was 60-70 calories per hour.

The heat lost by radiation and conduction was determined by noting the changes in the temperature of the calorimeter and the changes in the temperature of the air that passed through it. The heat lost by evaporation of water was measured by determining the quantity of water given off

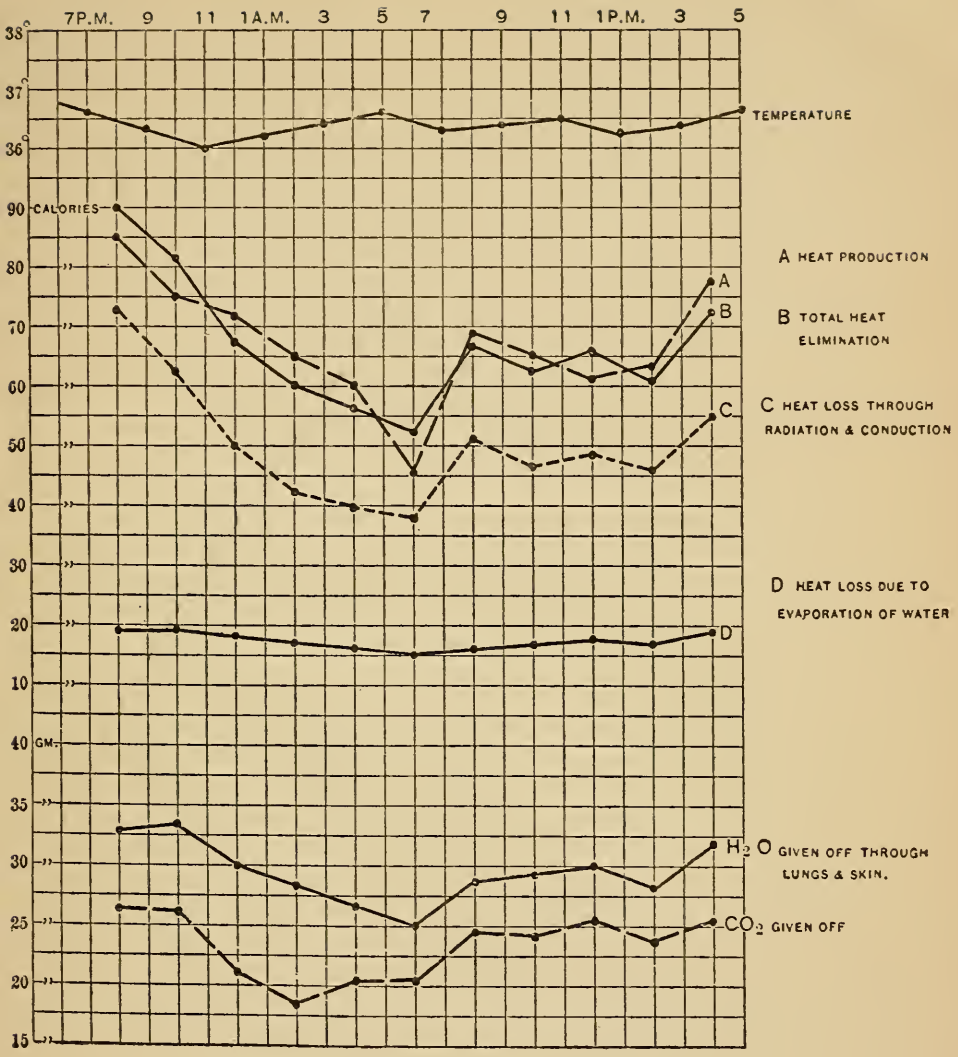

FIG. 13.
Normal day (Lehacheff and Avroroff from Ringer).

by the patient through her skin and lungs, and multiplying the same by 0.59 calories. The total heat production was obtained from the sum of the values of heat lost by evaporation of water and by radiation and conduction, plus or minus the retention or loss of heat because of changes in the body temperature. This last one was determined from the formula: $W \times (T \pm t) \times S$. W equals body weight, T equals temperature of the body, t equals value of change of temperature, and S equals specific heat of body, which equals 0.83. The patient was in the calorimeter for 3 days —one normal and two fever days. The results are seen in Figs. 13 and 14.

HEAT LOSS BY RADIATION AND EVAPORATION

Of the total sum of heat losses, the share of heat loss by radiation and heat conduction is 1.104 calories, or 74.6%, and the share of heat loss by evaporation is 376 calories, or 25.4%.

GASEOUS EXCHANGE

The elimination of Co_2 followed approximately the same order as did the development and loss of heat within the organism, namely, during evening hours, 7 to 11, the elimination of Co_2 stood at the maximum height, 26.5 grams per hour, then during the night (early morning) hours it fell to 18 grams and during the day hours an average of about 25 grams per hour. The night minimum of elimination of Co_2 was reached earlier than heat production and heat loss of the organism, so that at this time when the development of heat within the organism still continued to lower, the elimination of Co_2 already started on its rise.

WATERY VAPOR

Watery vapor, maximum 33 grams per hour in the night, it gradually came down to its minimum, 24.5 grams, and then during the morning hours would rise up to its

former height. The amount of absorbed oxygen during 22 hours was equal to 406 grams, and the respiratory quotient was 0.92.

The amount of N eliminated in the urine during 24 hours was equal to 11.4 grams. During fever days, Miss Zarerski ate but little (incomplete hunger) and she lost weight.

FEVER OBSERVATIONS

The stage of increase of fever was five hours and the period of decrease of fever about five hours. The chill commenced at 2 A. M. The temperature normally was 36.1°, and then rose to 37.9° and then to 39.3°, and at 7 P. M., was 39.7°, when the chill stopped. Then the temperature fell to normal by 11 o'clock, and from 11 to 12 the fever was over. The duration of the whole attack was about 10 hours. The period of the chill was about 3 hours.

Heat Production. During the period of

12-2 A. M., when there was no fever, and the patient in complete rest, there were 54 calories per hour. From 2-4 A. M., when patient was also asleep and woke up ¼ of an hour earlier than before, for she was disturbed out of her sleep for the purpose of taking the temperature, the heat production rose to 93 calories per hour, which coincided with the chill and rise of temperature, or the first stage of the fever. From 4-5 A. M., heat production rose to the maximum 112 calories, and the temperature rose to 39°, and the chill continued. During the succeeding 2 hours, from 5-7, heat production fell to 75-80 calories. After 7, the temperature began to fall and heat production at the same time fell to 56 calories; when sweat appeared, 8 to 10 A. M., the heat production gave a second wave, reaching 88 calories per hour, and then came down to its original level.

We see that heat production of our first observation in fever stands, until the be-

ginning of the attack and a few hours after the end of the attack, is lower than normal, owing to the diet. During the fever attack and immediately after the curve of heat production stands all the time higher than normal.

Heat production of the patient during the whole fever attack was considerably higher and the increase comes, almost without exception, from the period of rise of temperature.

General Heat Loss. From 12 to 2 A. M., when the patient slept, it stood at 65 calories per hour. During the following 2 hours, when the chill began, with a rise of temperature the heat loss was somewhat decreased, but not much, coming down to 56 calories. From 4-7 heat loss stood at its original level, although the temperature during that time reached 39.7°. After this temperature had reached its maximum, the heat loss began to rise quite rapidly, and by 8 reached 77, and by 9

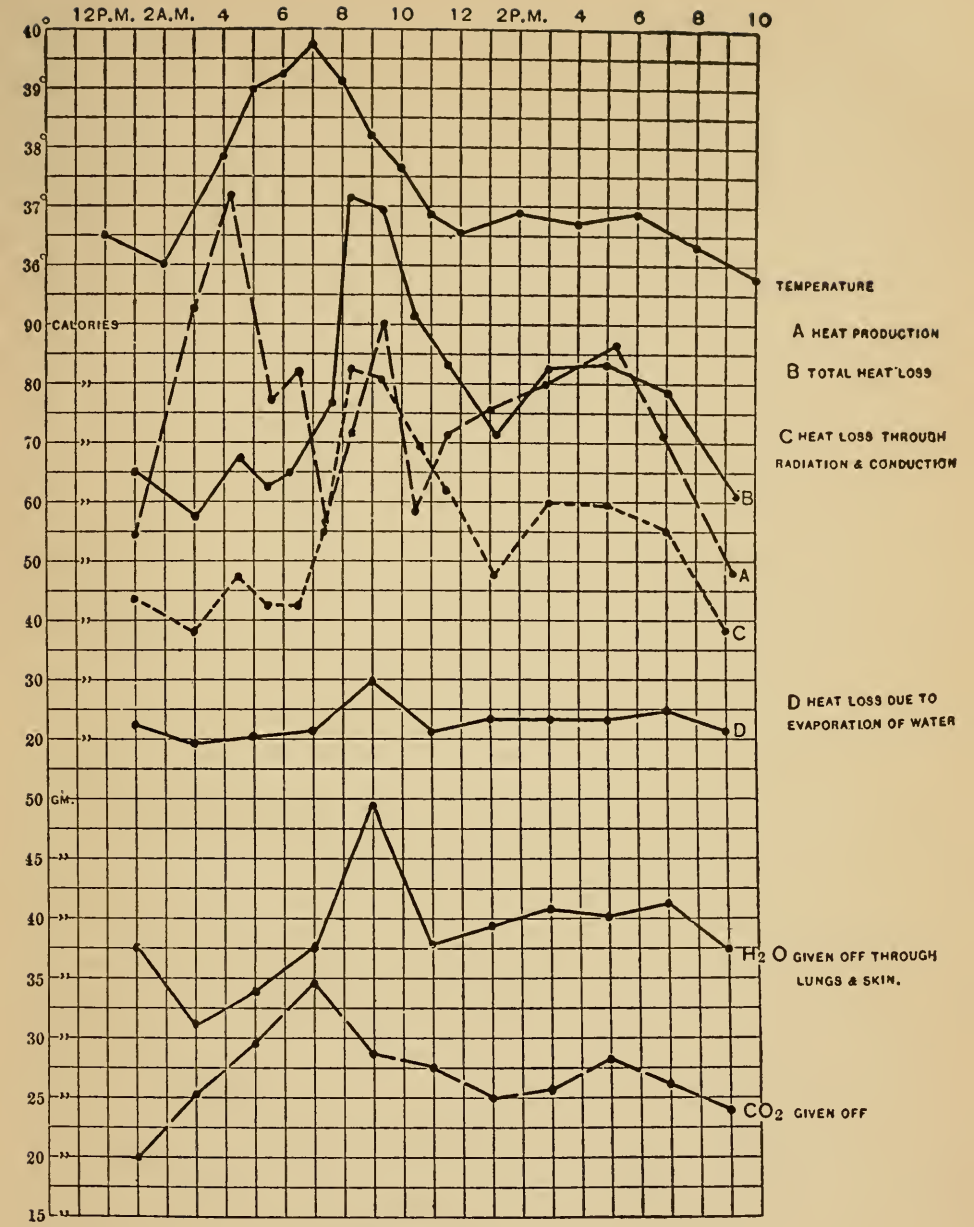

FIG. 14.

Day of high fever (Lehacheff and Avroroff from Ringer).

A. M., was up to 112 calories, double the original height. From 9 to 10, heat loss stood at the same height and by 2 o'clock it fell to 71 calories. From 2 to 6 P. M., it rose to 84 calories per hour, and after 8 P. M., when the patient was asleep, it came down to 60 calories, at about which level it stood at the very beginning of the observation.

Comparing the curve of heat loss with normal curve of heat loss, we see at the beginning of the fever attack, from 12-2 A. M., that heat loss stood at quite the same level as normal, and that during the first half of the attack, that is, during the rise of temperature of patient, the heat loss was somewhat higher than normal, since the curve of the normal day during these night hours coinciding with the time of sleep noticeably fell. During the second half of the attack, during the fall of temperature, the heat production rose much above nor-

mal, exceeding it almost one and a half times.

If we compare the curve of heat loss with the curve of heat production for the same fever day, we find both curves in their appearance are quite alike to each other; both during the fever have a quite sharp, but not lasting ascent, then a rapid fall and during the evening hours they rise again. But the differences in the curves are as follows: the curve of heat production during the fever attack gives but one wave, whilst heat dissipation curve gives at least two, from which the second wave, the one much lower in height, comes during the second half of the attack. The wave in the heat production curve, in time of appearance, precedes the same wave in the curve of heat dissipation by about 5 hours. The increase of heat production occurs at the very beginning of the attack, at the time of rapid rise of temperature, but the increase

of heat dissipation is observed only in the second half of the attack, during the fall of fever temperature and the fall of heat production which by that time succeeds in coming down to normal and gives a second rise coinciding in time with the appearance of the principal wave of heat loss.

In the increment of temperature the decrease of heat dissipation either played no part at all or played a very insignificant part. Here the rise of temperature in the patient was owing to the increased development of heat in the body, and the decrease of it was conditional upon an increased heat dissipation during the second half of the attack.

Heat Loss by Evaporation of Water from Skin and Lungs. It was higher than normal during the whole 24 hours. During the night and morning the heat loss by evaporation was 20 calories per hour, and in the afternoon about 24 calories. From 8 to 10 A. M., it rose from 20 to 29 per

hour, and after 10 hours it fell to 22 calories. The maximum of heat loss coincided with the appearance of sweat. The minimum heat loss by evaporation from skin and lungs was 19-20 calories per hour, coincided and took place from 2-6 A. M., that is, just during the period of chill.

Gaseous Exchange. Before the fever attack, during sleep, the elimination of Co_2 stood at a very low quantity, 20 grams per hour. Then with the rise of temperature and heat production, the elimination of Co_2 began to rise noticeably and gradually rose to 34 grams, which coincides in time with the highest point of temperature from 6 to 8 A. M., though heat production fell by this time considerably. With the fall of temperature during the second half of the attack, the elimination of Co_2 rapidly diminished too, and only in the afternoon showed, like the heat production, a temporary increase. There was a parallel in the curves between heat production and

the elimination of Co_2; a similar state was also seen normally. There was no correspondence between the curve of elimination of Co_2 and that of heat dissipation.

Absorbed Oxygen. The amount of oxygen absorbed for 22 hours was equal to 563 grams and the respiratory quotient was 0.75. The absorption of oxygen in fever was higher compared with the normal in an average for 22 hours.

Nitrogen. The amount of N eliminated with the urine during the 24 hours was 10.2 grams less than normal.

Their general deductions (after the second experiment with the same patient), were as follows:

	Max. Temp.	For 22 hours H.P.	Co_2	Ho_2	O_2	R.A.
Normal	36.0—36.6(C)	1.48 calories.	513	637	406	0.92
Mild fever 2nd observation	37.9	1.492 "	520	638	474	0.80
Severe fever 1st observation	35.8—39.7	1.633 "	587	852	563	0.76

In both observations, during the whole fever period there was observed a distinct

increase of both heat production and heat loss, and the increase of heat production occurred almost without exception during the rise of temperature and an increase of heat dissipation occurred during the period of decline of temperature.

In both of their fever observations there was a distinct rise of gaseous exchange; the increase of elimination of Co_2 was mainly during the period of rise of temperature and the elimination of water was sharply raised during the period of fall of temperature.

They also made experiments upon themselves while working under normal conditions. The mechanical labor consisted in lifting a weight of one pound (about 36 lbs.) standing upon a stool at a height of 60 centimeters, and letting it down to the floor for 2 hours after a previous rest of 2 hours, then a rest of 4 hours.

They found that under physiological conditions the organism can considerably

increase within itself the production of heat without causing thereby any substantial rise of its own temperature. Hence, they infer that the fever rise of temperature in a strictly physical sense depends chiefly upon the rise of heat production. From a physiological point of view we see in this fact that a very substantial part is undoubtedly played by the thermo-regulating facilities of the organism.

METABOLISM IN FEVER

Hirsch and Müller have shown that as the liver has the highest temperature, the greater metabolic changes must be found in this organ. The question then arose, whether after puncture of the thermogenic centers in animals freed of glycogen there ensued an elevation of temperature. Rolly found that in twenty-one rabbits with no glycogen in the muscles or liver, puncture of the thermogenic center did not cause an

elevation of temperature. In two rabbits only was there a rise of 0.4 and of 0.2° Fahrenheit. To animals free of glycogen he fed simple sirup to produce glycogen again; puncture of the brain then produced fever. In glycogen-free animals the injection of bacteria (pneumococcus and bacterium coli) produced a fever; hence in glycogen-free animals infection generates fever, but in the same animal thermogenic puncture does not.

Rolly also found that albumoses and peptones do not generate fever in glycogen-free animals. Ott [1] proved that they generated fever in animals in normal condition.

Rolly also found that there was no increase (or only a small one) of urinary nitrogen after thermogenic puncture in glycogen-free animals. Hence Rolly supports Krehl and Schultz in their theory that the small increase of urinary nitrogen after

[1] *Jour. of Physiol.*, 1887, VIII, 218.

brain puncture is due to the hyperthermia and is not a direct result of the puncture of the thermogenic center. In the glycogen-free animals not only does the thermogenic puncture produce no fever, but the increase of urinary nitrogen does not take place to any extent. Rolly believes that in neurogenic fever the increase of urinary nitrogen is due to the hyperthermia and not to the irritation of the thermogenic nerves. The greater increase of urinary nitrogen in fever generated by bacteria is due to an increased destruction of protein produced by the infection itself. In infectious fever there is from the beginning an abnormal destruction of proteid.

Hirsch, Müller and Rolly hold to the theory that in fever we have two parallel processes: (1) a specific breaking up of the proteid by the bacteria, and (2) a central excitation in the sense of a neurogenic fever.

Aronsohn has opposed this view. He believes that the increased destruction of proteid is dependent upon the nerves and ferments. The theory of a toxic destruction of proteid is without foundation. An increased destruction of proteid ensues according to him (1) where there is a paucity of glycogen and fats; (2) in toxic fever and in excessive irritation of the nerves, and (3) in cachexias. The increased destruction of proteid, according to Aronsohn, is a result of the fever-process due to heightened innervation of the cells—an irritation of a thermogenic center.

Senator and Richter (1) found results differing from those of Hirsch, Müller and Rolly. They also, by means of strychnia, made animals free of glycogen, and then made a puncture into a heat center, corpus striatum, which was followed by a temperature nearly as high as in animals with glycogen. They inferred that glycogen was

not necessary to the generation of fever and no special substance was needed to produce hyperthermia.

Ott and Scott [2] have studied the effect of an agent, tetra-hydro-beta-naphthylamine, upon glycogen-free animals. This body is a pure nervous agent in the production of fever. One of us has in another place [3] shown that it acts only when the corpus striatum and tuber cinereum are present. If only the corpora striata are removed, still the irritations of the thermogenic centers in the tuber by it are sufficient to produce a fever.

We did not find it an easy matter to free the animal completely of glycogen, but we had some with complete absence of glycogen either in the liver or muscles.

We showed that tetra-hydro-beta-naphthylamine will produce fever in a glycogen-

[2] Ott and Scott. *Journal of Experimental Medicine*, Vol. IX, No. 6, 1907.

[3] Ott. *Medical Bulletin*. 1898. XX. 411.

free animal. The fever here must be due to a using up of the protein. The metabolism of the protein is set into activity by the stimulation of the thermogenic centers in the corpus striatum and the tuber cinereum, for the removal of these centers prevents the naphthylamine from causing a rise of temperature.

Naphthylamine is a powerful thermogenic stimulant like the poisons of infectious fevers. Here the naphthylamine stimulates the nerve centers to act upon the protein, initiating changes in it. These facts do not support the views of Krehl and Rolly that puncture of the brain acts only on glycogen, while the infectious fevers produce a toxic metabolism of protein.

Nearly all observers agree that in fever there is an increased protein metabolism, but no increased fat metabolism except such as may result from inanition in the individual. There is every reason to be-

lieve that in both puncture of the thermogenic centers and in the infectious fevers, fever is produced by an action on the thermogenic centers.

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PROTEIN METABOLISM

Dr. Lusk, from 250 experiments upon dogs, in speaking of the specific dynamic action of food stuffs, found that the cause of it lay not in the absorptive or excretive mechanisms but in the interplay between the living cells and the nutrient material, the sugars and amino-acids in the blood. There was a marked increase in heat production after the ingestion of sugar, but in the 4 to 5 hours the heat production regained the level of basal metab-

olism. He believes the cause of this increased heat production to be due to the mass action of the sugar molecules reacting upon the liver cells. When alcohol was added to the glucose the heat production was raised above the level to which glucose alone would have raised it, and the alcohol was oxidized in preference to the carbohydrates. Lusk also studied three amino-acids convertible into sugar and urea and found that they could be given without appreciable increase of heat production. The result that followed the administration of amino-acids was like that which occurred after meat ingestion, in that the amount of increase of heat production was proportional to the quantity metabolized. He holds the view that the great increase in heat production is due to stimulation of the protoplasm to higher activity through the mass action of accumulated amino-acids. He also believes that the highest heat production is coincident with the

highest metabolism of amino-acids, and that the amino-acids themselves do not lie in the tissues to act as stimuli without being involved in highly active metabolism. It was shown that specific intermediary acids were formed in metabolism. These were the real stimuli, and when ingested protein was reconstructed into body protein the amino-acids involved in this reaction did not cause an increase in heat production. It might be stated that living cells metabolized carbo-hydrates and fats in increased quantity when these were present in large amounts in the surrounding fluid, and that they were also stimulated to a higher heat production during metabolism of certain amino-acids to an extent entirely out of proportion to their energy value.[4]

High temperature by itself increases the metabolism of proteins. Pflueger has estimated that for every increase of 1 degree

[4] *Med. Record.* 1914. June 27. P. 1189.

C in a rabbit's temperature, the heat production increases about 6 per cent., and the same has been found to be true for man when subjected to artificial heat. But this is only one cause of the increased production of heat in hyperthermia.

The infectious fevers have an increased nitrogenous metabolism. In an animal in starvation an equilibrium of metabolism is easily obtained. The nitrogen in the urine readily gives the amount of protein consumed, and albumen administered by the mouth easily keeps up a nitrogen balance.

In May's experiments upon rabbits the nitrogen after intravenous injection of a broth of bacillus of swine erysipelas, the temperature was 39.5 and nitrogen output 1.79; on the fourth day the temperature was 41.2° C. and nitrogen output 1.81; and on the fifth day it was 41.2 to 40.7, nitrogen output 2.45 grams.

In Staehlin's experiments dogs were in-

oculated subcutaneously with the trypanosome of Surra. The animal was in a condition of nitrogen equilibrium; it was kept in the Pettenkofer respiration apparatus and the output of nitrogen, carbon and water determined. He also made calorimetrical valuations of the food, urine and feces. Muscular work was avoided.

During the 1st fever day the dog took all his food, yet the outgo of nitrogen exceeded the in-go by a considerable amount. From the 4th to 7th day of the fever, the output of nitrogen was 44% above the nitrogen of the ingesta. From the 7th day to the 10th day, the output of nitrogen was higher than in the normal period, although the amount of food was diminished, and from the 10th to 12th days—the terminal days—the nitrogen deficit was on the 10th day 7.1 grams, and then diminished to one-half this amount. According to these figures the animal lost about 20% the original nitrogen present in the body.

Sharpe and Simon [5] found in a case of malaria that there was a tendency for the rise of temperature to be accompanied by an increased output of total nitrogen and less uniformly of creatinine. In two dogs, in whom the fever was preceded by rigor, the output of uric acid was increased.

Shaffer [6] has shown that the giving of large amounts of carbo-hydrates on a low protein diet may completely, or almost completely, maintain the patient in nitrogen balance throughout the disease.

There is no parallelism between the amount of nitrogen in the urine and the temperature of the body. Pribram and Robitschek and subsequently Fürbringer and Zuelzer found that the elimination of sulphur to a certain extent ran parallel with the variable urinary nitrogen.

Salkowsky further found that the in-

[5] Sharpe and Simon. *Journal of Experimental Medicine*, Vol. XX. No. 3, p. 282.

[6] Shaffer. *Journal Am. Med. Association*, 1908, Vol. 51, p. 974.

creased outgo of nitrogen was accompanied also by an increased elimination of potash salts.

Leathes also found in hospital patients that the creatinine was increased in fever. Linsen and Schmid found the purin bodies, ammonia and amino-acids, increased.

Graham and Poulton[7] by means of a chamber of heated steam elevated their temperature to 104° F., but notwithstanding the temperature there was no increase of metabolism by the high temperature.

Shaffer and Coleman[8] found that in typhoid fever, with an abundant diet of fat and carbohydrates, there was a nitrogenous equilibrium with a low intake of protein.

Kocher[9] has shown that a very liberal diet of as much as 80 calories per kilogram did not retard the protein metabolism of

[7] Graham and Poulton. *Quarterly Journal Med.*, Oct., 1912, p. 8.

[8] Shaffer and Coleman. *Archiv. Int. Med.* 1908, p. 538.

[9] Kocher. *Archiv f. Klin. Med.* 1914. CXV. 82.

typhoid fever in the early period of typhoid, as they did later. He holds that the protein destruction is due to the action of a special toxic substance upon protoplasm.

Coleman [10] has also found that food does not increase the heat production or temperature in typhoid fever, even when given in large amounts, at least where the quantity of protein is kept relatively low. A liberal diet in fever will not raise the temperature. He also found that just as in health, the body uses carbohydrates in preference to fat or protein to meet the increased demand for energy in typhoid fever. This teaches the necessity of a predominance of carbohydrates in the diet of a typhoid fever patient.

Causes of Protein Destruction. It is not alone increased temperature but also a toxic destruction of protein which increases the metabolism of protein in fever.

[10] Coleman. *Journal Am. Med. Association.* Vol. LXIII. No. 4. 1914. P. 932.

The intracellular ferments also act upon the increased amount of amino-acids and break them up and thus produce an increased elimination of nitrogen.

CARBO-HYDRATE METABOLISM

It was found out by May and Weber that the breaking up of protein may be reduced by giving carbo-hydrates. Hence it is probable that with the increased destruction of protein in fever, the glycogen also undergoes consumption at the same time. All the glycogen is consumed in the first few days of fever, and thus partially increases heat production.

METABOLISM OF FATS

The fats like the glycogen are also attacked in fever, but preferably the glycogen. Experiments lead to the idea that the gradual wasting of the fat is not due to any direct action on the fats, but rather to partial hunger. Staehelin does not be-

lieve that the using up of fat is entirely due to partial starvation.

WATER METABOLISM

In fever, conduction and perspiration-evaporation are lessened; the functions of dissipation do not act to maintain equilibrium at the same level, whether production of heat is normally increased or decreased. The continuous vaso-constriction reduces conduction and radiation of heat from the skin. The cause of fever, vaso-constriction, proceeds from the interior. The perspiration is lessened, and here we have another source of diminished radiation of heat. The water from the lungs is not diminished in fever.

Schwenkenbecker and Inagaki [11] show that insensible perspiration in fever is as great as in health, and that there is no accumulation of water in the body, as held

[11] Schwenkenbecker u. Inagaki. *Archiv. f. Exp. Path. u. Pharmakol.* 1906. B. 54, p. 168.

by Von Leyden. However, the urine is decreased in quantity.

Lang [12] has shown that the elimination of sweat is diminished during the elevation of temperature in man, but becomes normal at the height of the fever, whilst in some cases there is increased evaporation from the lungs.

In Staehilin's dog infected with surra, the total intake of water was 9030, whilst the total outgo was 11225, making an increase of 21955, or calculated by metabolism, 1880. There was certainly no retention of water here.

Von Noorden states that in fever the organism eliminates by the lungs more water, even during fasting, than a healthy individual does after a meal; the augmentation amounts to about 50%. The increase is, however, small.

[12] Lang. *Archiv. f. Klin. Med.* 1903. Band 79, p. 343.

PURIN METABOLISM

It was shown by Erben that xanthin bodies and animo-acids are increased in fever but in a degree varying with the character of the disease.

A. R. Mandel [13] found in so-called aseptic or surgical fevers that there is a large increase of the purin bases in the urine of patients fed with milk. The temperature rises and falls with the quantity of purin bases eliminated. Mandel also showed that subcutaneous injection of 40 milligrams of xanthin caused a marked rise in the temperature of a monkey, and that a strong decoction of 60 grams of coffee caused slight fever in a man not used to it.

Ott and Scott [14] found guanin, adenin and hypo-xanthin caused an elevation of

[13] Mandel. *American Journal of Physiology.* 1904. Vol. X, p. 452.

[14] Ott and Scott. *The Medical Bulletin.* Oct., 1907.

temperature in rabbits, whilst uric acid did not.

ACETONE BODIES AND ACIDS IN FEVER

Beta-oxybutyric acid, diacetic acid and acetone have been found in the urine of patients with increased temperature, but of the three bodies acetone is more frequently present.

It was noted by Regnard and Geffert and also by Minkowski and Kraus that the amount of carbon dioxide in venous blood was diminished. It was supposed to be due to increased formation of acid in the body. Ammonia was also increased, and it would lead us to think that there was an acid poisoning.

CHLORIDES AND PHOSPHATES IN FEVER

Redtenbacher first noted a retention of chlorides in the body, and this has been confirmed by several observers.

In pneumonia it was found that the

amount of sodium chloride in the urine was very greatly diminished before the crisis. After the crisis, it is excreted to a considerable extent. Von Limbeck, Schwarz, Von der Berg and Moraczewski regard the chloride excretion as inversely proportional to that of phosphoric acid, that retention of chlorine takes place in consequence of increased phosphoric acid elimination, the retained chloride keeping up an isotonic condition in the blood.

Fever consists of at least two main characters—thermogenic and toxogenic. As to the temperature, there is an agent which deranges the harmony of the thermo-inhibitory, thermogenic and thermolytic apparatuses, by which in the initial stage the metabolism of the tissues is usually temporarily increased and this increment is usually greater than that genated upon a restricted amount of nutriment. It is during the chill that heat

dissipation is temporarily diminished, but afterwards it usually follows the fluctuations of heat production. The tuber cinereum and the corpus striatum play the most important part in the thermogenic process and of these two the tuber is more important. Neither increased production nor diminished dissipation are necessary to constitute fever, as is shown where heat production diminished although the temperature is elevated. In another experiment of mine on lower animals, at one period the temperature was subnormal, yet the heat production was greatly increased above that seen on a similar period of the preceding day. As to the other symptoms in fever, they are caused by the toxines, chemical substances affecting every cell.

The toxines stimulate the cells causing increased metabolic change and consumption of energy. Hence the true theory of fever is a neurotoxogenic process.

That there is no increased production of heat in the stages of continued fever, but only a disarranged regulation of heat is quite evident to anyone who has stood by the bedside of a typhoid fever case in its terminal stages, with a high temperature, when the body looks more like a cadaver than like a living being throbbing with the fullness of blood and life. To imagine, despite the paucity of food, the wasting of the cells of the muscles and of the viscera, the fever is due to increased production of heat is ridiculous.

IS FEVER NOXIOUS OR BENEFICIAL?

It has been shown by Rolly and Meltzer [15] and Luedke [16] that animals heated up to 40°, after receiving daily subcutaneous injection of one-fourth to one-half the fatal dose of either staphylococci, pneumo-

[15] Rolly and Meltzer. *Deutsch. Archiv. f. Klin. Med.* 1908. XCIV. 335.

[16] Luedke. *Deutsch. Archiv. f. Klin. Med.* 1909. XCV. 425.

cocci or bacilli coli communis, lived longer, and one-half of them survived, whilst all the control animals died.

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